CONTENTS FOR DECEMBER, 1955

South Atlantic Association of Obstetricians and Gynecologists
Transactions of the Seventeenth Annual Meeting
Williamsburg, Virginia, February 10, 11, and 12, 1955

Original Communications

(*Continued on page 8*)

Nalline® HYDROCHLORIDE

(NALORPHINE HYDROCHLORIDE, MERCK)

Specific and effective therapy for narcotic-depressed newborns

MAJOR ADVANTAGES: Promptly increases both minute volume and respiratory rate; does not induce convulsions.

In neonatal apnea due to maternal narcosis, NALLINE may be injected directly into the umbilical vein of the infant to combat the depressant effects of the narcotic. This specific treatment promptly re-establishes respiration and in most cases usually eliminates the need for other methods of resuscitation. NALLINE may also be used prophylactically. When administered to narcotized parturient women five to fifteen minutes before delivery, NALLINE causes a significant decrease in the incidence of neonatal apnea requiring revival measures. At the same time, NALLINE appreciably shortens the time for first gasp and the time for establishing respiration.

OTHER INDICATIONS: Respiratory depression and circulatory collapse due to morphine, heroin, methadone, Dromoran®, Levo-Dromoran®, Nisentil®, Dilaudid®, Pantopon®, and Demerol®.

SUPPLIED: In 1-cc. and 2-cc. ampuls (5 mg./cc.), for parenteral use. NALLINE comes within the scope of the Federal Narcotic Law.

NEW DOSAGE FORM: NALLINE Neonatal for injection via the umbilical vein. In 1-cc. ampuls containing 0.2 mg. N-allylnormorphine hydrochloride.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

REFERENCE: Eckenhoff, J. E. and Funderburg, L. W., *Am. J. M. Sc.* **228**: 546, November 1954.

CONTENTS (*Continued from page 6*)

(Editorial and Business Communications on page 42)

American Journal of Obstetrics and Gynecology

Editors: HOWARD C. TAYLOR, JR., and WILLIAM J. DIECKMANN

American Journal of Obstetrics and Gynecology

VOL. 70 DECEMBER, 1955 NO. 6

South Atlantic Association of Obstetricians and Gynecologists

Transactions of the Seventeenth Annual Meeting, Williamsburg, Virginia, February 10, 11, and 12, 1955

SEX REVERSAL IN PSEUDOHERMAPHRODITISM*

ROBERT B. GREENBLATT, M.D., AUGUSTA, GA.

(From the Department of Endocrinology, Medical College of Georgia)

IN THE lower forms of life, in some species, such as worms, hermaphroditism remains a permanent condition throughout life. In others, such as the frog, the hermaphroditism is transitory. According to Browster[1] hermaphroditism has left an indelible imprint on the ladder of evolution. In such birds as the phalarope, Sir Peter Chambers Mitchell[2] has observed that the functional females have the secondary characteristics and habits of the male. The baneful legacy of hermaphroditism occasionally crops up in man.[1]

The term "hermaphroditism" is derived from Hermaphroditos, one of the minor Greek divinities. Symbolic of half-man, half-woman, Hermaphroditos was merely the continuation of legend. From being the objects of worship and veneration, such unfortunate humans later became the objects of scorn and derision. The latter-day Greeks cast them into the sea. Legend has it that a cock was sentenced and burned at the stake in Basle (1474) for the heinous and unnatural crime of laying an egg. (It was thereabouts, too [Geneva, 1553], that Michael Servetus, discoverer of the pulmonary circulation, was burned at the stake.) Until recent times, the management of the intersexes has

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

been faulty in that the efforts were directed toward restorative measures according to the gonadal sex. The approach to the problem has changed drastically. It is now generally conceded that much more may be accomplished if the psychic sex, rather than the genetic or apparent sex, becomes the prime consideration when hormonal or surgical procedures are undertaken.[3]

Sex reversal in pseudohermaphroditism is a provocative phrase which requires amplification and definition. Cawadias,[4] the distinguished Anglo-Greek physician who contributed considerably to the problem, rejected the older erroneous views on true and false hermaphroditism and suggested that the generally accepted classification of Klebs be abandoned. The term "intersexuality" is preferable for it connotes imperfect sex differentiation. The essayist is in full agreement with Cawadias on this point; nevertheless, the terms "male pseudohermaphroditism" and "female pseudohermaphroditism" are employed in this text because of their general usage at this time.

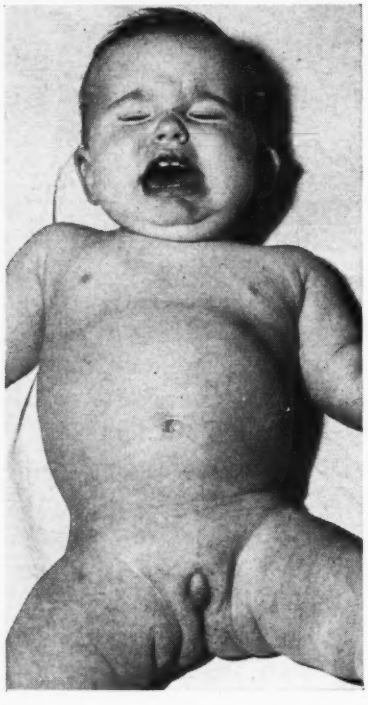


Fig. 1.—(Case 1.) Female pseudohermaphroditism due to congenital adrenal hyperplasia in a child 12 months old.

The term "sex reversal" may have one of several connotations: (a) Sex reversal, as used by Wilkins,[5] denotes the changes that occur as a result of some endocrine abnormality. (2) Sex reversal may signify the psychophysical alterations brought on by surgical procedures. (c) Sex reversal may refer to changes induced by hormonal therapy.

The purpose of this paper is threefold: (1) to share the experiences gained in the management of the intersexed patients studied by the Depart-

ment of Endocrinology at the Medical College of Georgia; (2) to present the diagnostic procedures employed; (3) to emphasize the importance of directing hormonal or surgical procedures, or both, to conform to the emotional and psychological trend, rather than to the gonadal sex of the patient.

Female Pseudohermaphroditism

The following 4 cases were selected from our group of female pseudohermaphrodites to illustrate various points in diagnosis and management in the different age groups, i.e., infancy, childhood, and adulthood. The approach was not the same in all cases.

Congenital Adrenal Hyperplasia With Addisonian Crisis in an Infant.—CASE 1.—This infant had a diagnosis of hermaphroditism at birth and was christened as a male because of a hypospadias of the penis (Fig. 1). Several months afterward, the child developed vomiting, diarrhea, dehydration, signs of collapse, and bronzing of the skin.

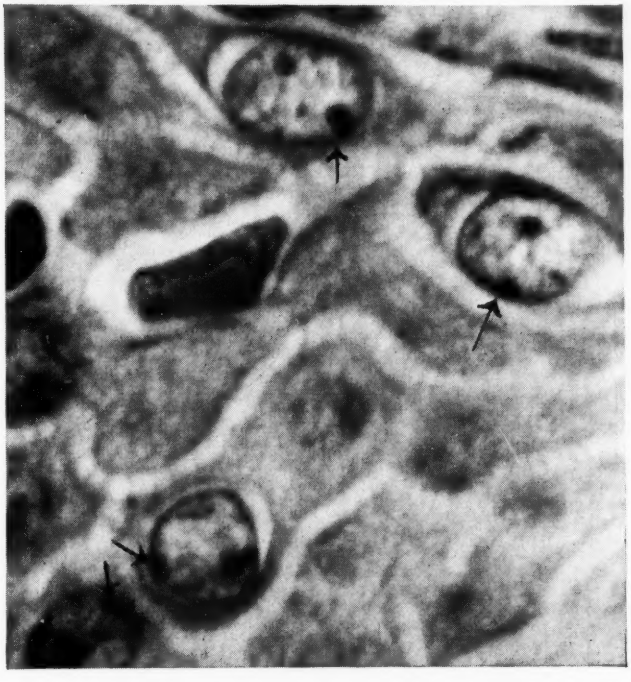


Fig. 2.—(Case 1.) Skin biopsy showing female nuclei configuration. Arrow points to sex chromatin positive nuclei.

Cortisone and desoxycorticosterone were used to bring the infant out of adrenal crisis, and maintenance doses of corticosteroids have prevented further setbacks. When, at the age of 12 months, the child was brought to the Medical College of Georgia for study, the following findings were considered pertinent:

1. Bone age = slightly delayed.
2. Urinary 17-ketosteroids[6] = 1.1 to 3.1 mg. per 24 hours.
3. Urinary 17-hydroxycorticoids[7] = 1.2 to 2.06 mg. per 24 hours.
4. Thorn ACTH test = eosinophil drop from 390 to 147 per c.mm.
5. Serum sodium = 123.9 meq. per liter; serum potassium = 4.81 meq. per liter.
6. Chromosomal sex skin[8] = female nuclei configuration—sex chromatin positive nuclei being 72.8 per cent of counted epidermal cells (Fig. 2).

Comment.—Congenital adrenal hyperplasia in female children leads to pseudohermaphroditism. Because of the altered adrenal cortical function, androgen-like steroids are produced at the expense of gluco- and mineralocorticoids, hence the tendency toward Addisonian crises in many of these cases. The delay in bone age in this patient, rather than an advanced bone age, may be accounted for by the early and satisfactory suppression of excessive 17-ketosteroid production by the adrenals through therapy with cortisone. The child described in Case 1 has now been under our observation for fifteen months. Satisfactory growth and development have taken place. The bone age remains slightly delayed. The parents, much to their chagrin, were advised to bring the child up as a girl and to change her name from "Jack" to "Jackie." Progressive feminization may be expected on continued cortisone therapy (5 to 10 mg. per day).

Fig. 3.—(Case 2.) Female pseudohermaphroditism due to congenital adrenal hyperplasia in a child aged 5 years.

Congenital Adrenal Hyperplasia in a Child.—

CASE 2.—This child, aged 5 years, though being reared as a female, was referred by her pediatrician for determination of the true sex (Fig. 3). An enlarged clitoris was present at birth; pubic hair had appeared at the age of 3½ years. The following findings were significant:

1. Urinary 17-ketosteroids = 25.6 mg. per 24 hours.
2. Urinary 11-oxycorticoids[9] = 0.14 mg. per 24 hours.
3. Allen test for dehydroisoandrosterone[10] = negative.
4. Thorn ACTH test = eosinophil drop from 162 to 62.5 per c.mm.
5. Bone age = advanced to 8½ years (chronologic age of 5 years).

Chart 1 summarizes the 17-ketosteroid values, the growth curve, and the bone age for the period of observation of 42 months.

Comment.—The presence of pubic hair, the advanced bone age, and the high 17-ketosteroids immediately stamp this child as a female. Under continuous cortisone therapy she

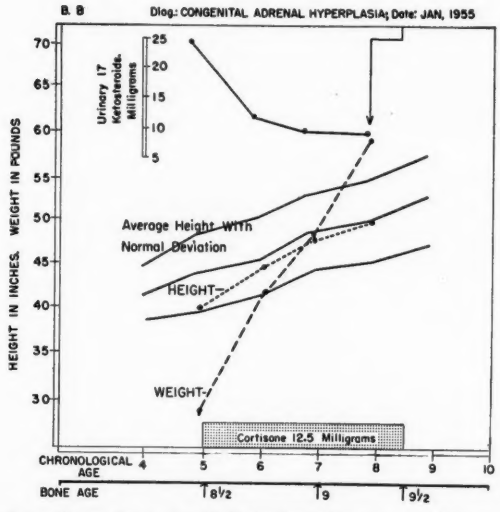


Chart 1.—(Case 2.) Note drop in 17-ketosteroids on continuous cortisone treatment over three and one-half years. Note also that the bone age has advanced only one year during this period of time and the height is within normal range.

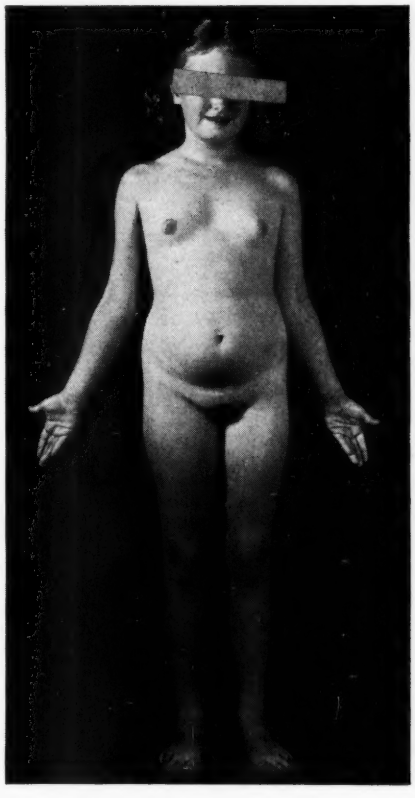


Fig. 4.—(Case 2.) Patient at age 8½ years (three and one-half years after start of cortisone treatment).

is growing normally in height, the breasts are enlarging somewhat prematurely, and the rate of bone development has been considerably slowed down. The size of the clitoris and the amount of pubic hair growth have regressed slightly. The child is being feminized, and her actions and attitudes are those of a normal female child (Fig. 4). The therapy consists of 12.5 mg. of cortisone daily, along with a high-protein, low-fat, low-carbohydrate, low-salt diet. Potassium chloride, 5 grains twice a day, is being administered to help maintain electrolyte balance.

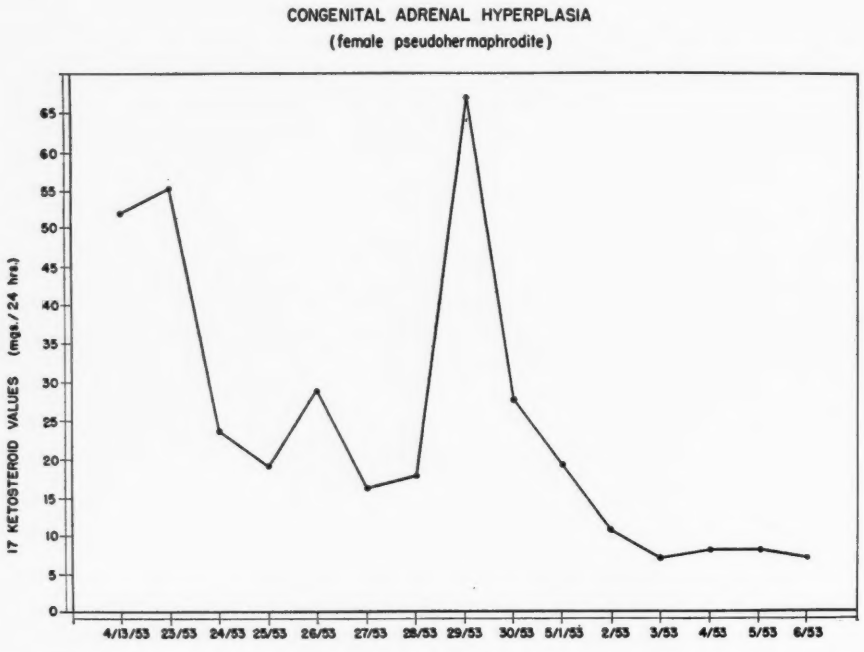


Chart 2.—(Case 3.) Note rapid drop in 17-ketosteroids to normal values on performance of cortisone test.

Congenital Adrenal Hyperplasia in an Adult With Epilepsy.—

CASE 3.—This 21-year-old female had a history of epileptic convulsions since the age of 6 months. The attacks occurred about once per week and sometimes more often. She had been shaving daily for many years. The voice had been harsh, the breasts were undeveloped, and the stature was diminished. The vaginal canal was well formed; the orifice was virginal. The clitoris was markedly enlarged. There was much hairiness of the extremities, chest, and abdomen. Scanty menses of one or two days' duration occurred at varying intervals of 5 to 10 months. The patient was feminine in her mannerisms and interests, though presenting a masculine appearance (Fig. 5). The following findings were significant:

1. Urinary 17-ketosteroids = 51.1 to 55.2 mg. per 24 hours.
2. Urinary 11-oxycorticoids = 0.94 mg. per 24 hours.
3. Vaginal smear = castrate.
4. Calcium = 10.3 mg.; phosphorus = 3.34 mg.
5. Electroencephalogram = grand mal tracings.
6. Cortisone test = drop in 17-ketosteroids from 55.2 to 7.7 mg. per 24 hours within two weeks on 100 mg. cortisone daily (Chart 2).
7. Chromosomal sex skin = female nuclei configuration.

Comment.—The patient has been on the required dietary regime and on 20 mg. of hydrocortisone three times daily for the past two years. She has become more feminized in that the breasts have enlarged (Fig. 6), the hypertrichosis has lessened considerably though she still shaves daily, and menses have become ovulatory, occurring at about 34 day intervals. The vaginal smear has matured to normalcy. Surprisingly, the epileptic seizures have decreased to such an extent that there is an interval of several months between attacks.

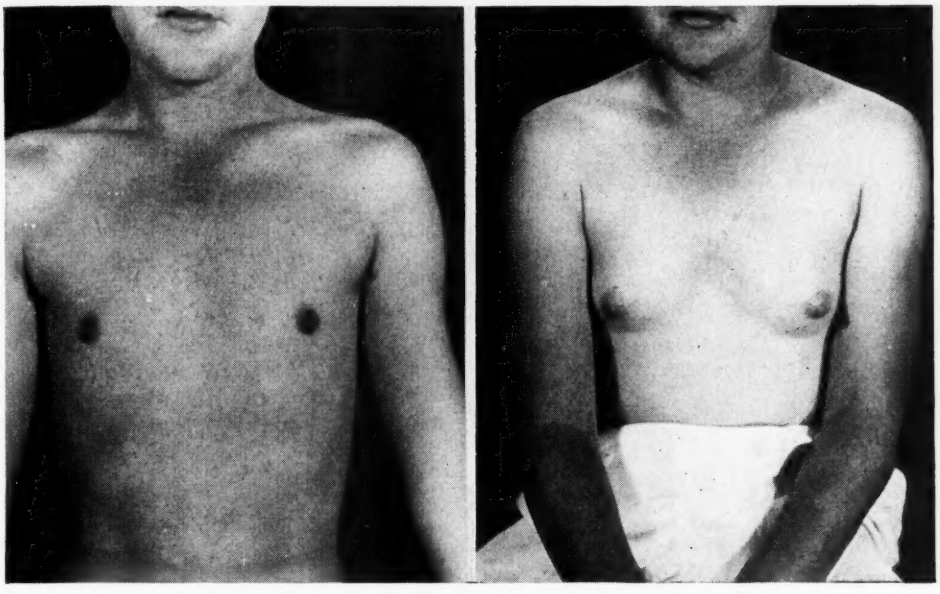


Fig. 5. Fig. 6.

Figs. 5 and 6.—(Case 3.) Congenital adrenal hyperplasia in adult 21 years of age, before (Fig. 5) and after cortisone treatment (Fig. 6). Note breast development and loss of chest hair (Fig. 6).

Congenital Adrenal Hyperplasia in an Adult Female With Excessive Virilization.—

CASE 4.—This 32-year-old patient had rapid growth until the age of 12 years when linear growth stopped. On examination the patient was of diminished stature (56¾ inches), muscular, and completely masculine in body physique. Cephalic alopecia, and hairiness of the chest, abdomen, and extremities were present (Fig. 7). The clitoris was markedly enlarged. The urethra, which had been previously dilated by sounds, occupied the site of the vaginal canal (Fig. 9). An exploratory laparotomy had been done and small ovaries, uterus, and Fallopian tubes were found. Histologic study of an ovarian biopsy showed ovarian tissue.

Psychiatric opinion was obtained and the masculine drives of the patient confirmed. The aptitudes and attitudes of the patient were entirely masculine, and she wished to be transformed into a male. The pertinent findings were as follows:

1. Urinary 17-ketosteroids = 120 to 175 mg. per 24 hours.
2. Urinary 11-oxycorticosteroids = 0.92 mg. per 24 hours.
3. Urinary FSH = less than 9.7 to more than 19.3 M.U. per 24 hours.
4. Urinary pregnanediol[11] = 10.3 mg. per 24 hours.
5. Perirenal insufflation = moderate enlargement of right adrenal gland; no evidence of tumor.

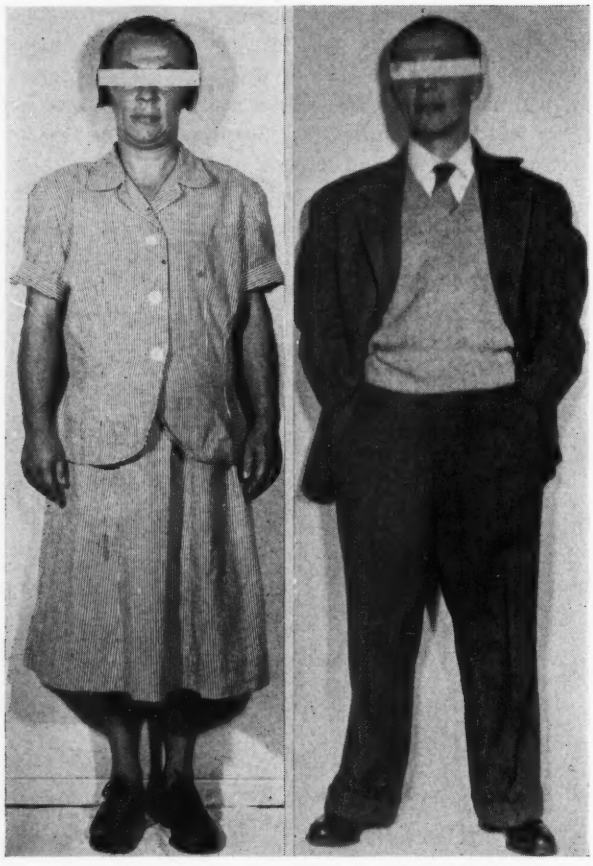


Fig. 7. Fig. 8.

Figs. 7 and 8.—(Case 4.) Congenital adrenal hyperplasia in an adult female with excessive virilization. Before (Fig. 7) and after transformation (Fig. 8).

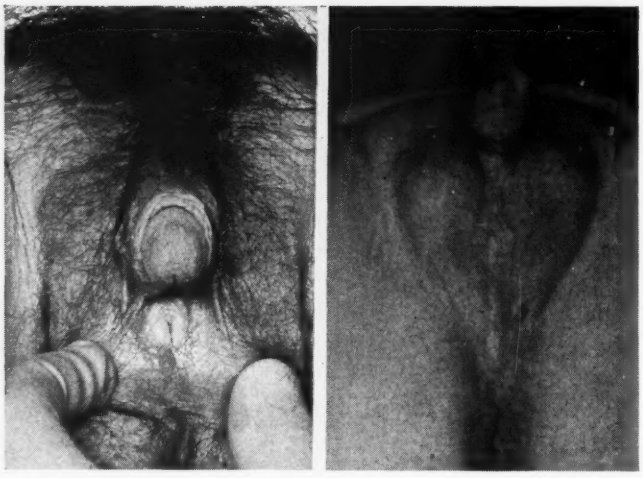


Fig. 9. Fig. 10.

Figs. 9 and 10.—(Case 4.) Before (Fig. 9) and after reconstruction of external genitals (Fig. 10). Fig. 10 shows results of canalization of freed phallus and implantation of plastic spheroids.

Comment.—After psychiatric, urologic, and legal consultations were obtained, the opinions were unanimously in favor of masculinizing this patient. Surgical measures were then undertaken to complete the genital masculinization. Fig. 10 shows the results of freeing the clitoris, canalizing the penis, and implanting plastic spheroids into each labium majus so as to give the impression of a scrotal sac. The results have been excellent in every way (Fig. 8). The patient has made a most satisfactory adjustment and is now able to enjoy feminine company, have erections, void at a urinal instead of being seated, and the guilt complex of being attracted to other females has been dissipated. Legal change in name and status have followed.

Male Pseudohermaphroditism

Two cases of male pseudohermaphroditism have been selected from our group of patients to illustrate certain points and pitfalls in management.

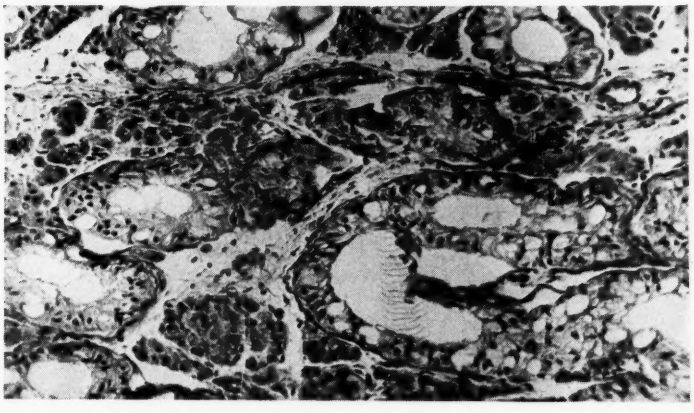


Fig. 11.—(Case 5.) Histologic study of testis shows normal Leydig cells and tubules lined only by Sertoli cells.

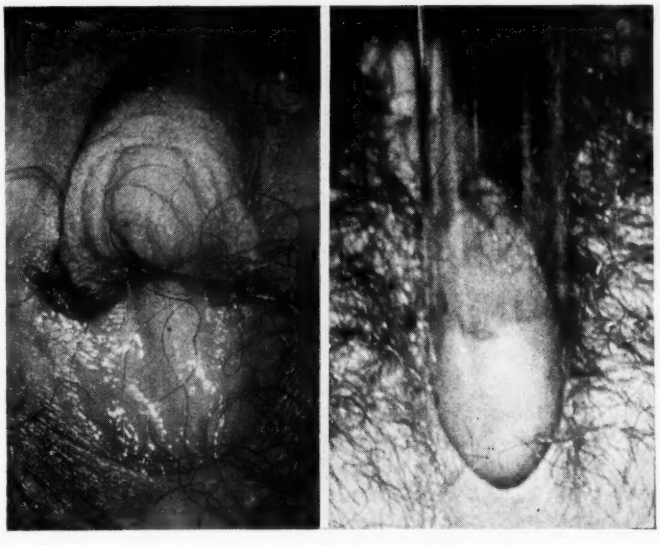


Fig. 12. Fig. 13.

Figs. 12 and 13.—(Case 5.) Note enlarged clitoris and absence of vaginal introitus (Fig. 12). Indentation exercises with test tube succeeded in producing a vaginal canal 6 cm. deep, as shown in Fig. 13 with test tube in place.

Intersexuality in an Individual Raised as a Female.—

CASE 5.—A young woman, 16 years of age, began to question the absence of menses, the changing of her voice, the appearance of facial hairiness, the lack of breast development. Examination revealed a rather tall, slender individual with hypospadias of the penis and absence of a vaginal canal. The patient was definitely feminine in her psychological make-up and it was decided to help her toward femininity by surgery and hormonal therapy. Urinary 17-ketosteroids assayed 20.3 mg. per 24 hours. At laparotomy, abdominal testes were removed. Study of histologic sections revealed numerous Leydig cells, but the tubules were lined only by Sertoli cells (Fig. 11). The phalluslike structure was excised, labia were formed, and a vaginal canal was started by indentation of the perineum just above the fourchette. With the aid of an inverted test tube, indentation exercises were carried out by the patient daily. A few years after treatment was begun, the test tube could be inserted into the vaginal canal for a distance of 6 cm. (Figs. 12, 13). On intermittent estrogen therapy the breasts have developed and the vaginal mucosa has become estrinized. Most of the facial hair has disappeared and the patient is now a rather beautiful female, enjoying male companionship. She is feminine in her habitus, attitudes and aptitudes (Fig. 14).

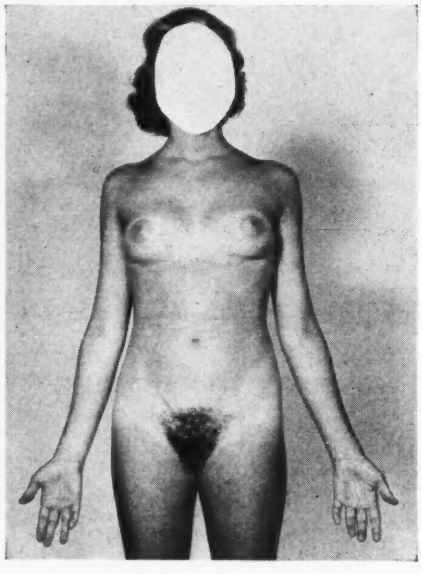


Fig. 14.—Case 5.) Male pseudohermaphrodite after three years of treatment with cyclic estrogen therapy. Note excellent breast development and feminine contour.

Comment.—Experience has taught that male pseudohermaphrodites, as a rule, fare better as females than as males. With few exceptions, the surgeon or urologist would do well to discourage reconstructive procedures designed mainly to conform to the gonadal sex. A case in point to illustrate the folly of attempting to convert a male pseudohermaphrodite into a functional male is that of an 18-year-old boy who now begs to be "unsexed" and transformed into a female. This particular patient was brought up as a girl until the sixth year of age, and then as a boy thereafter. At 15½ years of age, a urologist decided to reshape him because laparotomy had revealed the presence of abdominal testes. The physician disregarded the presence of gynecomastia, the effeminate nature of the patient, the beardlessness, and the high-pitched voice. The breasts were removed and six operations were performed in an attempt to bring the testes down and to correct the hypospadias. The attempts were futile for the patient is now completely inadequate as a male (Fig. 15). He is sterile, lacks masculine drive and interests, and is psychologically and emo-

tionally feminine. In retrospect, it is not difficult to see that reconstructive surgery toward maleness should not have been undertaken. The patient should have been allowed to progress toward femaleness. The abdominal testes might have been removed and estrogens administered to accentuate development in the female direction. A vaginal canal could have been created and the small phallus removed. Experience has shown that such effeminate intersexuals rarely become adequate males, regardless of how well the surgery is performed or the amount of androgen administered.

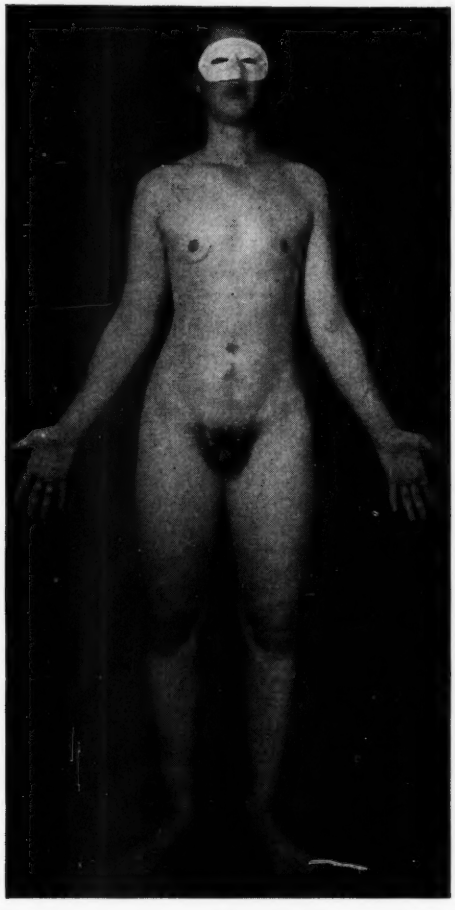


Fig. 15.—Mismanagement of male pseudohermaphrodite. Unsuccessful attempt to masculinize this patient by reconstructive surgery. Note scarring from bilateral mastectomy. The testes are atrophic and remain high in poorly developed scrotum.

Unsuspected Male Pseudohermaphroditism in a Completely Feminized Individual.—

CASE 6.—This patient was an apparently well-developed female 21 years of age (Fig. 16). Her only complaint was amenorrhea. Examination showed excellent breast growth, scanty pubic hair, no hypertrichosis, normal clitoral development, and a well-formed vaginal canal which ended in a blind pouch. Two inguinal scars were noted, representing repair of bilateral inguinal hernias some four years previously, at which time a gonadal mass (testicle) was removed from the right hernial sac.

Present studies revealed male sex skin chromatin configuration. The urinary 17-ketosteroid assay was 17.6 mg. per 24 hours. The bone age was normal. The vaginal smear was only slightly hypoestrogenic. Laparotomy was performed and a left abdominal testis

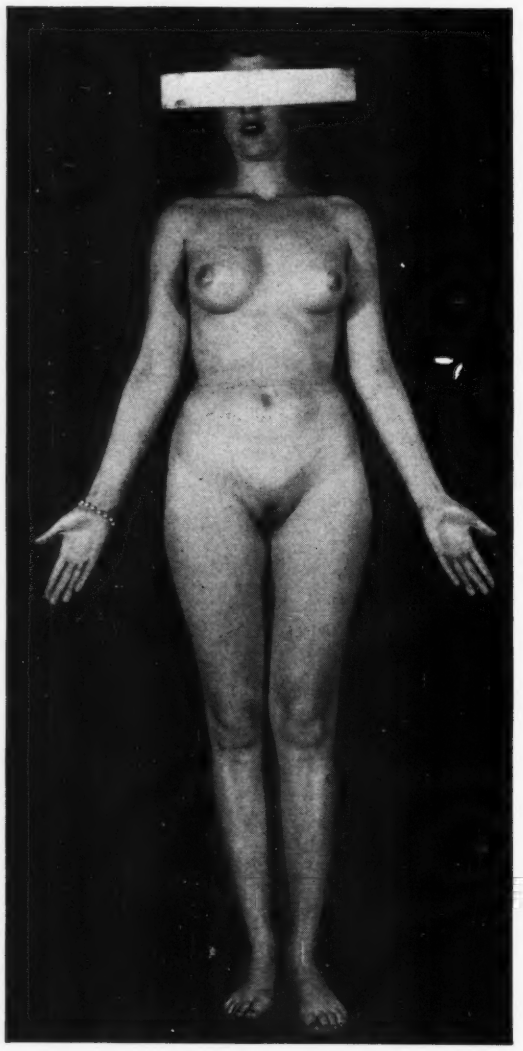


Fig. 16.—(Case 6.) Unsuspected male pseudohermaphroditism in completely feminized individual.

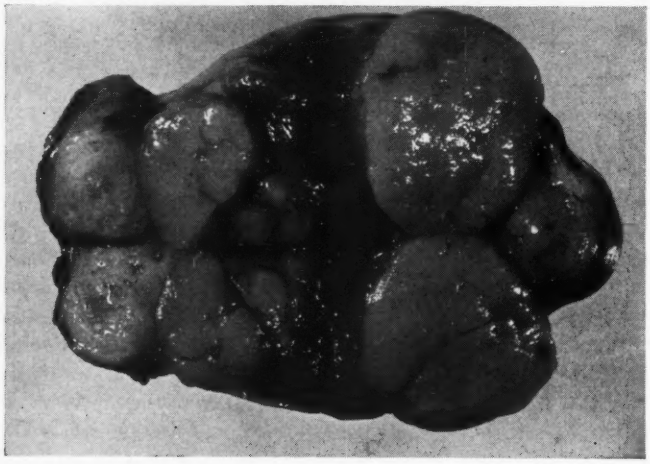


Fig. 17.—Appearance of bisected abdominal testis removed from Case 6. Note tumor nodules.

was removed. Three pellets of estradiol (25 mg. each) were implanted under the rectus muscle. Sectioned surfaces of the bisected testicular specimen revealed multiple tumor nodules (Fig. 17) and on study of histologic sections multiple adenomas composed of immature tubular structure were noted (Fig. 18).

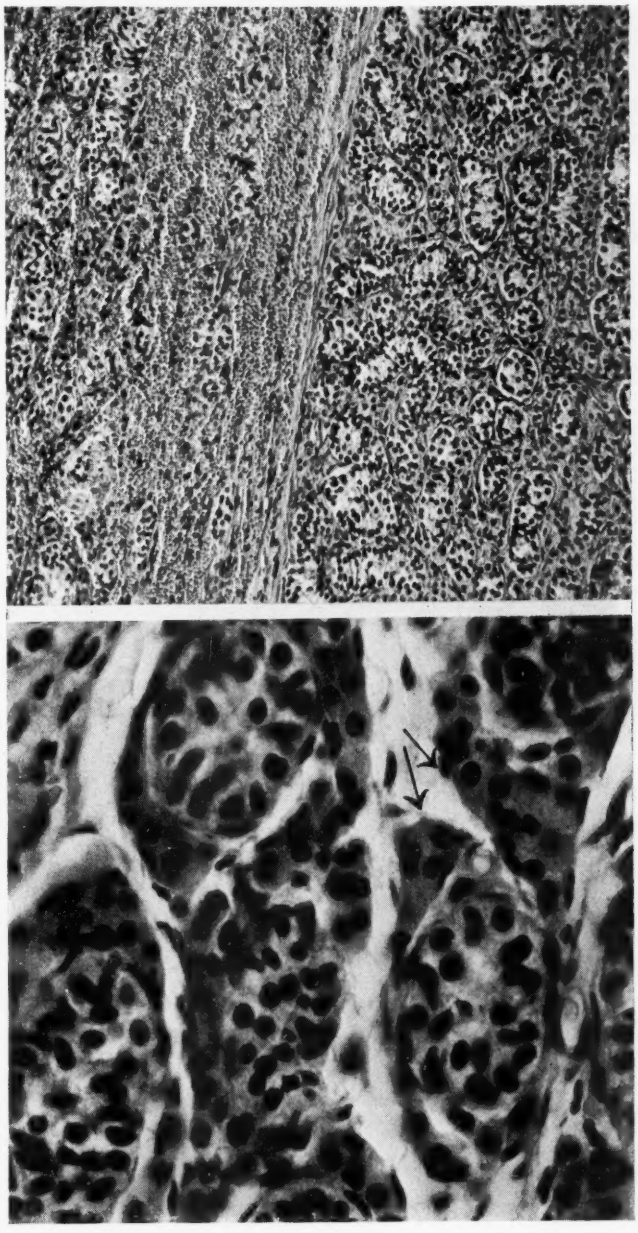


Fig. 18.—(Case 6.) Histologic section of testis shows circumscribed nodule diagnosed as adenoma tubulare (right, upper photomicrograph). Lower photomicrograph shows high-power field from nontumorous section of testis. Note the immature tubules. Arrow points to groups of Leydig cells.

Comment.—The marked feminization of this patient suggests that the testis may have been producing some estrogens. There is much controversy as to whether abdominal gonads should be removed. The findings in this case, however, lend substance to the argument that

abdominal testes should be excised, because the incidence of tumor formation is much greater than when the testes are in the normal site. The study of this patient emphasizes the fact that the sex of a pseudohermaphrodite cannot and should not be determined by the external appearance of the genitals. Infants who, at birth, present evidence of poor sex differentiation should not be immediately labeled male or female or given a permanent Christian name until studies are performed to clarify the sexual status. The appearance of the external genital pattern may too frequently prove a snare for the unwary.

Comment

The classification of individuals with imperfect sex differentiation may be simplified and more generally understood if the following categories are considered:

A. Female pseudohermaphroditism is the result of an endocrine disorder caused by excess hormone production as in congenital adrenal hyperplasia. Very occasional cases of female pseudohermaphroditism of genetic origin have been reported.[12] The sex chromatin distribution in the nuclei is always female. The gonadal sex is female.

B. Male pseudohermaphroditism is the result of an anatomic anomaly, genetic in origin. There is no primary endocrine disorder other than, at times, inadequate androgen production. The sex chromatin distribution in the nuclei is always male. The gonadal sex is male.

C. True hermaphroditism is a very rare occurrence. Only 49 cases have been recorded in the world's literature.[13] It is a genetic disorder. Either ovaries and testes, or one ovary and one testis, or ovotestes, are present.[14] There is no evidence of an endocrine disorder. The sex chromatin distribution in the nuclei may be either male or female.

D. Ovarian dysgenesis with androgenic manifestations is a form of hermaphroditism. The ovaries are agenetic. In some of these cases the ovaries have a cortex composed of ovarian stroma without primordial follicles and masses of Leydig cells in the hilus. These females usually have an enlarged clitoris. Two recent cases have been described by Gordon[15] and one patient who may be fitted into this category has recently been described by this author.[16] The sex chromatin distribution in the nuclei is usually male. Also related to this group is the female with ovarian agenesis (Turner's syndrome). Such patients, though not showing any androgenic manifestations, frequently have male sex chromatin distribution in the nuclei.[17, 18]

The management of female pseudohermaphroditism has been hormonal through the suppression of excessive production of androgenic hormones by the adrenal cortex.[19, 20, 21] Cortisone or hydrocortisone inhibits the pituitary adrenocorticotrophin and permits the adrenal cortex to remain at rest. It must be emphasized that, when cortisone-like compounds are administered, the proper dietary regime must be enforced. This includes a high-protein, low-carbohydrate, low-fat, low-salt diet. The addition of potassium chloride, 5 grains two or there times daily, to avoid electrolyte imbalance, is advisable. Frequent examinations of the patient are essential for signs of overdosage, i.e., rapid weight gain, increase in blood pressure, or the appearance of sugar in the urine.

The dosage of cortisone should be sufficient to lower the urinary 17-ketosteroid levels without inducing a Cushing-syndrome appearance, osteoporosis, or other complications.[22]

The male pseudohermaphrodite, if seen in early childhood, may be given a trial of chorionic gonadotropins in the hope of inducing descent of the testicles. Those who respond may be managed with a view to salvaging them according to their gonadal sex.[23] Those who do not respond, and those patients seen at a later age and showing feminine inclinations or being brought up as females, should be treated by surgical and hormonal methods in order to transform them in the female direction.[24]

Conclusions

1. A group of patients were selected from the 25 pseudohermaphrodites studied at the Medical College of Georgia in order to illustrate certain points in diagnosis and management, as well as in mismanagement.

2. The psychic make-up of the individual, rather than the gonadal sex, should be the decisive factor in determining the direction in which the transformation should be made.

3. At birth, infants who present evidence of imperfect sex differentiation should not be immediately labeled with a definite Christian name until studies are performed to clarify the sexual status. The appearance of the external genitals should not be the criterion upon which to base a diagnosis of "male" or "female" in these cases.

4. Sex reversal and development along more normal lines are possible through the feminizing effect of cortisone in congenital adrenal hyperplasia, and through operation in the excessively virilized females. In the male pseudohermaphrodites, surgery to reconstitute the male should be reserved for the really few masculinized patients. Otherwise, castration and excision of the clitoris, when indicated, with formation of a vaginal canal by minor surgical procedures, appear to be the method of choice. Intermittent but persistent estrogen therapy is advisable to enhance vulvovaginal maturation, breast development, and body contour. The social rehabilitation and psychological adjustment, as a rule, prove gratifying. Effeminate pseudohermaphrodites never quite make the grade as adequate males, in spite of androgens and the best that surgery has to offer.

The author acknowledges with thanks the assistance of Dr. Eve Marberger of the State University of Iowa College of Medicine in the interpretation of skin biopsies for sex determination. He also wishes to acknowledge the urologic reconstructive work done by Dr. Robert Rinker in Case 4.

Grateful acknowledgment is made to the following pharmaceutical companies for supplies of medications used in this study:

The Upjohn Company—Cortisone acetate and hydrocortisone (Cortef)
Merck & Co., Inc.—Cortisone acetate and hydrocortisone (Cortone and Hydrocortone)
Schering Corporation—Estradiol pellets (Progynon)
Ciba Pharmaceutical Products, Inc.—Desoxycorticosterone acetate (Percorten) and ethinyl estradiol (Eticylol)
Ayerst, McKenna and Harrison, Ltd.—Estrone sulfate (Premarin)

References

1. Browster, L. R.: Endocrine Man, New York, 1945, Grune & Stratton.
2. Mitchell, Sir P. C.: Foreword, Endocrine Man, New York, 1945, Grune & Stratton.
3. Creadick, R. N.: South. M. J. **46**: 455, 1953.
4. Cawadias, A. P.: Hermaphroditos, ed. 2, London, 1946, William Heinemann, Ltd.
5. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., 1950, Charles C Thomas, Publisher.
6. Drekter, I. J., Heisler, A., Scism, G. R., Stern, S., Pearson, S., and McGavack, T. H.: J. Clin. Endocrinol. **12**: 55, 1952.
7. Reddy, W. R., Jenkins, D., and Thorn, G. W.: Metabolism **1**: 511, 1952.
8. Moore, K. L., Graham, M. A., and Barr, M. L.: Surg., Gynec. & Obst. **641**: 96, 1953.
9. Daughaday, W. H., Jaffe, H., and Williams, R. H.: J. Clin. Endocrinol. **8**: 166, 1948.
10. Allen, W. H., Hayward, S. J., and Pinto, A.: J. Clin. Endocrinol. **10**: 54, 1950.
11. Stimmel, B. F., Randolph, J. D., and Conn, W. M.: J. Clin. Endocrinol. **12**: 371, 1952.
12. Melicow, M. M., and Cahill, G. F.: J. Clin. Endocrinol. **10**: 24, 1950.
13. Fischer, H. W., Lischer, C. E., and Byers, L. T.: Ann. Surg. **136**: 864, 1952.
14. Smith, F. R.: Northwest Med. **52**: 1022, 1953.
15. Gordon, G. S., Overstreet, E. W., Traut, H. F., and Winch, G. A.: J. Clin. Endocrinol. **15**: 1, 1955.
16. Greenblatt, R. B., and Carmona, N.: J. Clin. Endocrinol. (In press.)
17. Poloni, P. E., Hunter, W. F., and Lennox, B.: Lancet **2**: 120, 1954.
18. Wilkins, L., Grumbach, M. M., and Van Wyck, J. J.: J. Clin. Endocrinol. **14**: 1270, 1954.
19. Wilkins, L., Lewis, R. A., Klein, R., Gardner, L. I., Crigler, J. F., Rosemberg, E., and Migeon, C. J.: J. Clin. Endocrinol. **11**: 1, 1951.
20. Wilkins, L., Crigler, J. F., Silverman, S. H., Gardner, L. I., and Migeon, C. J.: J. Clin. Endocrinol. **12**: 277, 1952.
21. Jailer, J. W., and Louchart, J.: J. A. M. A. **150**: 575, 1952.
22. Jones, G. E. S., Howard, J. E., and Langford, H.: Fertil. & Steril. **4**: 49, 1953.
23. Greenblatt, R. B.: AM. J. OBST. & GYNEC. **66**: 700, 1953.
24. Finkler, R. S.: J. Clin. Endocrinol. **8**: 88, 1948.
25. Evans, T. H., and Riley, G. M.: Obst. & Gynec. **2**: 363, 1953.

Discussion

DR. BAYARD CARTER, Durham, N. C.—The studies of pseudohermaphroditism and of adrenal hyperplasia have two things in common. First, these patients should have the benefit of a full diagnostic survey which includes hormonal, urologic, and gastrointestinal investigations and also radiologic study of the bones including the spine. Second, they must have competent psychiatric evaluation.

This psychiatric evaluation is in our opinion the most important part in deciding upon therapy for the patient. It is our belief that the obstetrician-gynecologist should be present during this psychiatric evaluation because only by doing so may he comprehend the problem.

All therapy, be it hormonal, operative, or a combination of the two, is predicated upon the psychiatric evaluation.

Since hormonal therapy and operative therapy are now fairly well understood for these patients, the psychiatric evaluation remains our one guide in formulating future programs for them. The type of gonad found was not necessarily the influencing factor in rehabilitating these patients in either the male or female direction. This is an important point with which we agree.

FURTHER OBSERVATIONS ON THE EXPECTANT MANAGEMENT OF PLACENTA PREVIA*

JOHN Q. HATTEN, M.D., SAMUEL A. KIRKPATRICK, M.D., AND W. NORMAN THORNTON, JR., M.D., CHARLOTTESVILLE, VA.

(From the Department of Obstetrics and Gynecology, School of Medicine, University of Virginia)

IN THE past decade the expectant management of placenta previa has become an accepted method of treatment in some cases. In 1947 Williams[1] reported his observations on the management of placenta previa in 105 patients treated in the University of Virginia Hospital. Forty-one patients in this group were followed expectantly with a loss of only 5 infants. This infant mortality rate of 12 per cent included the deaths of 4 premature infants and of one mature infant who died of congenital malformations incompatible with life.

More recent reports by Mills,[2] Macafee,[3] Johnson,[4] and Neilson[5] have confirmed the soundness of this method of management for some patients with placenta previa. Better pediatric care of liveborn premature infants in the past ten years has increased the survival of these infants as shown by Neilson and Neilson,[5] whose mortality rate of liveborn premature infants has decreased from 50 to 20 per cent in the period from 1942 to 1953. This study is concerned with the results obtained by pursuing essentially the same policy, as outlined by Williams,[1] in 59 additional patients with placenta previa seen in the University of Virginia Hospital from Jan. 1, 1947, through Oct. 31, 1954. During this period there were 13,236 deliveries.

Classification

The patients with placenta previa have been divided according to the newer classification which was agreed upon by Greenhill, Titus, McCormick, and Eastman at a conference held in 1949. According to this classification, all previa are divided into total, partial, or low-lying placentas as shown in Table I. The classification as to degree of previa, however, does not take into consideration the actual location of the placenta and this may be of considerable significance in determining the type of delivery, as pointed out by Stallworthy.[6] A placenta of the partial or low-lying type located on the posterior surface of the uterus, over the promontory of the sacrum, may reduce the capacity of the inlet. Under such circumstances rupture of the membranes may not effect engagement of the head to control bleeding, and prolapse of the cord may occur. This latter accident occurred in one patient who was being evaluated under a double setup. Immediate cesarean section was done with delivery of a viable infant who survived. Fig. 1 illustrates the placenta located in the posterior segment of the uterus with marked anterior displacement of an unengaged vertex.

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

TABLE I. CLASSIFICATION

Total previa	22	37%
Partial previa	10	17%
Low-lying placenta	27	46%
Total	59	100%

Diagnosis

The diagnosis of placenta previa was established by determining the location of the placenta at the time of cesarean section or by palpation of the placenta on vaginal examinatioin, with the exception of two instances in which placentography was unequivocal. X-ray visualization of the placenta was employed in 33 patients and was accurate in locating the placenta in 21 of them. We believe soft-tissue x-ray studies are valuable in the differential diagnosis of bleeding in the third trimester, and the method described by Reeves and Cahoon[10] should make soft-tissue visualization of the placenta more accurate. X-ray visualization of the placenta is most helpful and valuable in excluding placenta previa in some patients with third trimester bleeding. The possibilities of demonstrating the placenta in a patient with suspected previa with a previable fetus should be exhausted before resorting to vaginal examination. The value of soft-tissue x-ray studies is to some degree proportional to the obstetrician's interest and experience in the interpretation of these studies.

Treatment

The methods of management and delivery of the 61 infants of 59 mothers are shown in Table II. The incidence of cesarean section has increased to 57 per cent, whereas it was 42 per cent in the old series. It is to be noted that delivery was accomplished by version and extraction on 4 occasions. The location of the placenta was low-lying previa in each instance of version. Three of the infants were premature, weighing less than 2,000 grams, and the fourth weighed 2,970 grams. Only one infant survived. This is a hazardous procedure for mother and child. We feel that if the problem cannot be managed vaginally, by amniotomy or scalp traction following amniotomy, delivery should be effected by cesarean section.

TABLE II. METHOD OF TREATMENT

	NO.	PER CENT
Cesarean section	35	57
Amniotomy	7	11
Scalp traction after amniotomy	4	7
Spontaneous onset of labor and vaginal delivery	11	18
Version*	4	7
Total	61	100

*Including version on second twin.

Maternal Statistics

There were no maternal deaths in this group of 59 patients with placenta previa. There were 51 multigravidas and 8 primigravidas. It is interesting to note that 10 patients did not require blood replacement. However, an average of 1,650 c.c. of whole blood was required for each of the 59 patients from the time of admission to the hospital until discharge from the hospital, following delivery. One patient required 5,500 c.c. of whole blood.

Fetal Statistics

The uncorrected perinatal mortality was 26.2 per cent as shown in Table III. Three of the 32 infants delivered at term did not survive. One infant was deadborn, having been delivered by version and extraction as a heroic measure after prolapse of the umbilical cord. The second infant died of congenital cerebral defects incompatible with life. The third infant died of atelectasis some twelve hours after delivery in which amniotomy and scalp traction had been employed.

TABLE III. PERINATAL MORTALITY WITH PLACENTA PREVIA

METHOD	NO.	TERM			PREMATURE		
		LIVED	STILL-BORN	NEONATAL DEATH	LIVED	STILL-BORN	NEONATAL DEATH
Spontaneous	11	4	0	0	3	2	2
Amniotomy	11	4	0	1	4	2	0
Cesarean section	35	21	0	1	8	0	5
Version	4	0	1	0	1	1	1
Total	61*	29	1	2	16	5	8

*Including two sets of twins.

Fig. 1.—Illustrates the placenta located in the posterior segment of the uterus with marked anterior displacement of an unengaged vertex.

The survival rate was disappointing in the group of 29 premature infants, including one set of twins. Thirteen of these premature infants did not survive when labor was spontaneous, or the pregnancy was terminated before the child had reached a weight of 2,500 grams. The deaths of 5 premature infants occurred in association with delivery by cesarean section, done on the basis of

continued vaginal bleeding. In 4 patients premature labor was spontaneous and resulted in delivery of 4 deadborn infants. An additional deadborn infant was delivered after version in a multipara who was in premature labor with spontaneous rupture of the membranes. Neonatal death from atelectasis accounted for the remaining 3 deaths in the group of 13 premature infants who did not survive.

The perinatal mortality rate of 45 per cent in the group of 29 premature infants is somewhat better than the rate of 68 per cent shown in our first series. Improved pediatric care of the premature infant probably accounts for the increased survival in the current series.

Regardless of the type of delivery in placenta previa, prematurity remains the greatest hazard to the infant, as shown in Table IV. It is to be noted that there were only 4 deaths in the group of 44 infants who weighed 2,000 grams or more.

TABLE IV. PERINATAL MORTALITY IN RELATION TO INFANT WEIGHT

WEIGHT	CESAREAN SECTION		VAGINAL DELIVERY	
	NO. OF INFANTS	NO. DIED	NO. OF INFANTS	NO. DIED
Less than 1,000 grams	0	0	2	2
1,000-1,499 grams	2	2	2	1
1,500-1,999 grams	4	2	7	5*
2,000-2,499 grams	7	1	5	0
2,500 grams plus	22*	1	10	2
Total	35	6	26	10

*Including twin pregnancy.

Expectant Management

Does expectant management accomplish anything? In an attempt to answer this question we have critically studied the records of 24 patients of this series of 59 patients who were managed expectantly as shown in Table V.

TABLE V. PERINATAL MORTALITY WITH EXPECTANT TREATMENT

METHOD	NO.	TERM 10		PREMATURE 14	
		LIVED	DIED	LIVED	DIED
Spontaneous	7	3	0	3	1
Amniotomy	3	0	0	2	1
Cesarean	13	7	0	3	3
Version	1	0	0	1	0
Total	24	10	0 (0%)	9	5 (36%)
Old series	41	31	1 (3%)	5	4 (44%)

The average duration of expectancy, or observation prior to delivery, in this group of 24 patients was 23.2 days. Ten infants weighing 2,500 grams or more were delivered and all survived. Of the 14 infants weighing less than 2,500 grams, 5 failed to survive.

One infant that weighed 922 grams was delivered after spontaneous onset of labor on the twenty-second day of observation. Another infant that weighed 1,725 grams was deadborn and delivered after the spontaneous onset of labor on the seventy-fifth day of observation for placenta previa. Of this group of 5 infants who did not survive, 3 were delivered by cesarean section. Labor was spontaneous in one of these patients and pregnancy was terminated by cesarean section in the remaining 2 because of continued hemorrhage. A central placenta previa was found in each of the latter 2 patients.

We believe we have been able to carry 7 infants from prematurity to maturity by this method of management. In addition, we believe that delay

of delivery was a factor in the survival of 12 infants. Expectant management was disappointing in 7 patients because of the spontaneous onset of labor resulting in the loss of 3 infants as previously mentioned. In 7 instances it appears that premature infants were delivered as a result of the physician's becoming alarmed by bleeding in the absence of labor. Two infants were lost in this group as noted.

Current methods of management of placenta previa indicate that this complication of pregnancy is not especially hazardous for the mother, but is associated with a high perinatal mortality rate, as shown in Table VI.

TABLE VI. MATERNAL AND FETAL MORTALITY RATES

AUTHOR	PATIENTS	YEAR REPORTED	MATERNAL MORTALITY %	FETAL MORTALITY %
Mills[2]	100	1948	0.00	16.5
Paalman and Hunt[7]	134	1949	1.5	23.0
Johnson[4]	201	1950	0.00	21.0
Stallworthy[6]	245	1951	0.4	18.0
Neilson[5]	220	1953	0.00	13.4
Schmitz[8]	112	1954	0.89	22.3
Williams[1]	105	1947	0.95	28.0
Present series	59	1954	0.00	26.2

There is another aspect of the problem which is of concern to the obstetrician and the pediatrician. Placenta previa is frequently associated with repeated uterine hemorrhage and varying degrees of shock may be encountered. In a recent study by Latham, Anderson, and Eastman,[9] it was found that uterine bleeding occurred at some time during the pregnancy in 39.3 per cent of the mothers of a group of 61 newborn infants who subsequently developed cerebral palsy. It was suggested that anoxia might be in part responsible for the brain damage in these infants. We have been able to follow each of our 45 infants whose mothers had placenta previa for periods varying from six weeks to six years, and fortunately none have shown evidence of cerebral palsy. We realize that six weeks is not sufficient time to rule out this condition. The findings, however, seem to suggest that the bleeding encountered in placenta previa is not associated with a high incidence of central nervous system damage in the infant who survives.

Summary and Conclusions

The management of 59 patients with placenta previa has been presented. Expectant management was followed in 24 patients in the group, and some factors contributing to the high perinatal mortality rate have been discussed.

The uncorrected perinatal mortality rate was 26.2 per cent in the 61 infants delivered of 59 mothers. The perinatal mortality rate for the infants of mature weight was 9.4 per cent, as compared with a rate of 45 per cent for infants of less than 2,500 grams.

It would seem that expectant management was a factor in the survival of 19 of the 24 infants whose mothers were candidates for this type of observation prior to delivery.

Expectant management is disappointing in some patients because of the spontaneous onset of labor, and in other patients it appears that the obstetrician has been somewhat hasty in terminating the pregnancy on the basis of continued or repeated episodes of bleeding.

References

1. Williams, T. J.: Am. J. Obst. & Gynec. **55**: 169, 1948.
2. Mills, W. G.: Brit. M. J. **2**: 896, 1948.
3. Macafee, C. H. G.: Post Grad. M. J. **25**: 297, 1949.
4. Johnson, H. W.: Am. J. Obst. & Gynec. **59**: 1236, 1950.
5. Neilson, R. P., and Neilson, D. R.: West. J. Surg. **61**: 184, 1953.
6. Stallworthy, J.: Am. J. Obst. & Gynec. **61**: 720, 1951.
7. Paalman, R. T., and Hunt, A. B.: Am. J. Obst. & Gynec. **57**: 900, 1949.
8. Schmitz, H. E., O'Dea, N. J., and Isaacs, J. H.: Obst. & Gynec. **3**: 3, 1954.
9. Latham, D., Anderson, G. W., and Eastman, N. J.: Am. J. Obst. & Gynec. **68**: 91, 1954.
10. Reeves, R. J., and Cahoon, J. B.: M. Radiog. and Photog. **28**: 2, 1952.

Discussion

DR. JOHN S. FISH, Atlanta, Georgia.—There is a faint hint of disappointment in the tone of this paper, and at first glance I, too, am somewhat depressed to note a 15 per cent increase in the incidence of section and only a 2 per cent drop in perinatal mortality since the original study. It is a mistake, however, when attempting a program of expectancy, to assume responsibility for its interruption by labor. It has been our experience that labor followed the initial episode of bleeding within 24 hours in 35 per cent of cases of placenta previa and in 51 per cent of cases of ruptured sinuses. During attempts at expectant therapy, the final cause for interruption was, indeed, labor in half the cases of placenta previa and all the cases of ruptured sinuses. Many babies have, however, been brought to maturity before labor intervenes.

Continuation of expectancy in the face of frequently recurring gross hemorrhages which may overextend our defenses against maternal risk cannot be too severely criticized, though we, ourselves, have, with rigidly controlled patients, outwaited as many as five hemorrhages. Thus, in 45 per cent of our placenta previa cases handled expectantly, either frequent gross hemorrhage or the final recurrence of hemorrhage close enough to term to minimize the problems of prematurity and the unfavorable cervix turned out to be the indication for termination. And the point here, likewise, is that many babies have passed the critical point in maturity before the intercession of such hemorrhage. Thus, before a halt was called by either of these factors, labor or hemorrhage, we were able to carry our patients with placenta previa 5½ weeks and with sinus ruptures 3½ weeks. The compensating truth in Dr. Hatten's series lies in the conclusion that, in 19 of 24 cases managed expectantly, delay in delivery was a factor in infant survival. The perinatal mortality with expectant management was 20.9 per cent and in cases not managed thus it was 31.4 per cent. This is anything but discouraging.

Only half, or less, of the so-called painless hemorrhages of late pregnancy are due to placenta previa. Most of the remainder originate from rupture of the marginal sinus of the normally implanted placenta. Expectant management is applicable to hemorrhage from either source. Delay of diagnostic vaginal examination until definitive treatment is needed is advantageous. Delay in examination is aimed at putting off so far as is possible the labor or hemorrhage responsible for premature termination and at working past the point where section will be a temptation, not because of true placenta previa, but simply because of hemorrhage and a bad cervix.

Intrauterine death in placenta previa may result from maternal shock or from critical pressure on the low-lying placenta or cord. That the latter is the chief cause is indicated by a stillbirth rate of zero in Dr. Hatten's abdominal deliveries, and in our series is strongly suggested by a stillbirth rate in placenta previa three times that in marginal sinus hemorrhages with normal implantation. Concentration upon prematurity should not lead us to overlook these figures. Keen judgment is required in selecting the proper delivery route to ensure that the gains made in expectant management are not, at the end, wasted in fetal asphyxia from compression. Stillbirths are a function of definitive treatment, but not of expectancy.

The cesarean section incidence of 57 per cent seems high, but I find it difficult to quarrel with this when 54 per cent of the cases are classified as total or partial placenta previa. This preponderance of the more severe degrees of previa prompts an interest in the over-all incidence of previa in the authors' work and the possibility that they have either deliberately eliminated from this study or inadvertently overlooked many cases of lesser degree. By comparison, our classification shows less than 30 per cent in the total-partial group. This difference is reflected in a section rate of 22 per cent and goes on to be reflected in a perinatal mortality of 7.5 per cent. I conclude that a comparison of these figures with Dr. Hatten's signifies nothing without a comparison of diagnostic criteria.

DR. ARTHUR L. RIVERS, Charleston, S. C. (Read by DR. JAMES WILSON, Charleston, S. C.)—Expectant treatment in selected cases of placenta previa has been gaining in popularity since Herman Johnson first referred to it in 1944. We agree that expectancy has its place in cases in which symptoms are minimal, the mother is in good condition, and sensible precautions can be taken.

The essayists are to be commended on their low mortality rate and the manner in which they handled their cases. There are several features in our treatment of placenta previa that differ from theirs, however.

1. We feel that a sterile vaginal examination is very important. It should be done gently and should include visual as well as digital exploration (not boring) into the cervix. The examination is done after adequate blood has been made available, in the delivery room with preparation to control bleeding, such as hydrostatic bags and Willett forceps at hand. An anesthetist also should be present. Such examination gives invaluable information that no other type of examination gives, and when done gently does not endanger mother or baby. We have seen patients with placenta previa with active bleeding and questionable labor admitted to the hospital with the cervix almost fully dilated, and consequently safely and quickly delivered from below. Further, careful evaluation of the cervix will aid in determining whether expectancy holds much hope of improving the chances of the baby. If the pregnancy cannot be continued at least a week nearer term we have not really benefited the baby. If the cervix has begun to be effaced and dilated labor will probably continue, and the danger to the mother of repeated hemorrhage outweighs the possible benefit of expectancy to the baby.

2. We are absolutely opposed to rectal examinations in any patient with bleeding in the last trimester. We do not allow such examinations because active and alarming bleeding may be precipitated, and no information can be gained.

3. We agree that cesarean section will naturally be much more frequently indicated in central previa, in primiparas, and in patients with unfavorable cervices or with malpresentations.

4. Hydrostatic bags still have their place in any discussion of placenta previa. We realize fully that the hydrostatic bag has lost a great deal of its popularity. We feel this is due mainly to: (a) dry rotting of the rubber and consequent leakage; (b) potential infection from more manipulation, trauma, etc.; and (c) lack of experience in its use. In using the bag, test it for leaks; choose a size that will allow delivery of the baby when it is expelled; insert it intraovularly by digital, not visual, guidance away from the placental site, and slowly fill it while the fingers still hold it in place. Check cervical dilatation frequently by rectal examination. If edema of the cervix begins, the bag should be removed. There will frequently be no more bleeding after it is removed because of sealing of sinuses, etc., by pressure. We have delivered many live babies and lost no mothers by using hydrostatic bags, and feel we would be letting an old friend down if we did not mention it.

While I cannot give accurate statistics as to fetal mortality, in our private practice I am glad to report that our maternal mortality in placenta previa cases is zero. Our plan

of treatment is neither rushing in, nor expectant in its scope. Fetal deaths have been mainly in cases of marked prematurity, but we do not feel that expectancy in its broadest sense would have improved our percentage of salvage.

We do not mean to imply that we are opposed to expectant treatment in placenta previa, but feel that the following factors have to be borne in mind before the best form of treatment is finally decided upon: (1) duration of pregnancy, (2) age and parity of patient (importance of fetal salvage), (3) condition of baby by fetal heart tones, (4) availability of blood, (5) availability of competent obstetrical care (medical and nursing), (6) presence of Rh incompatibility, (7) any deformity of baby (x-ray, etc.), (8) previous section prior to placenta previa, (9) very careful estimate of patient's physical condition, (10) consideration of previous pregnancy, labor, and puerperium, (11) mental attitude of patient to expectancy, and (12) last but not least, economic factors—hospital cost, employing extra help at home, need of professional donors.

In short, the most important factors in handling placenta previa are suitable hospital facilities, competent attending, proper diagnosis, available blood, minimal analgesia, proper choice of anesthesia, and treatment of minimal shock before it becomes irreversible so that mother and baby will not be jeopardized by the treatment chosen.

We should always bear in mind the well-known facts that: (1) The first hemorrhage in placenta previa is seldom if ever fatal, but subsequent hemorrhages may be fatal. (2) What would be minimal shock from blood loss in a nonpregnant individual can very quickly turn into irreversible shock in obstetrical patients. On these two premises alone we feel that medical students should continue to be taught that the pathognomonic triad of painless, causeless, recurring bleeding in the last trimester of pregnancy probably is placenta previa and spells serious trouble. Expectancy should be mentioned but not stressed as acceptable treatment.

DR. HATTEN (Closing).—In answer to Dr. Wilson's remarks concerning early sterile vaginal examinations, we feel that if we do sterile vaginal examinations early, then we may be in a position where we will have to do something about terminating the pregnancy right then and there. On the other hand, by carrying on the expectant plan, we feel we are able to prolong the pregnancy further.

CORRELATION OF ESTIMATED PROGNOSIS WITH SOME FINDINGS AND RESULTS IN 750 STERILE COUPLES*

VIOLET H. TURNER, M.D., CLARENCE D. DAVIS, M.D.,** AND BAYARD CARTER, M.D., DURHAM, N. C.

(From the Department of Obstetrics and Gynecology, Duke University School of Medicine and Duke Hospital)

THE sterility clinic at Duke University School of Medicine has been active for the last twenty years. Seven hundred and fifty *couples* have been completely studied. All couples who have completed their sterility survey have been included in this report. These couples have had one or more years of infertile mating without the use of any prevenception.

A sterility survey consists of a complete history of both husband and wife, and general physical and genital examinations, routine laboratory studies, basal metabolic levels, fasting serum cholesterol determinations, and any other special studies deemed necessary in both of them. Seminal examinations are carried out, preferably on two or more specimens. The wife has postcoition studies done at about the calculated time of ovulation, hysterosalpingography, and endometrial biopsy. The endometrial biopsy is taken as an office procedure with an endometrial punch or suction curette a few days before the expected time of menstruation or within the first 24 hours of bleeding. The woman is usually advised to use prevenception during the month in which biopsy is to be obtained. If possible, these examinations are repeated when the findings are abnormal. In the latter years of the study, most of the wives have taken their basal body temperatures rectally for varying periods of time. During the survey, both members of the couples are seen on two or more occasions. Following completion of the survey which usually requires two to three months, each couple is seen in conference. At the time of the conference, the couple's situation is discussed and questions are answered as forthrightly as possible. Therapy is outlined and an honest attempt is made to give the couple an estimated prognosis for pregnancy.

TABLE I. PREGNANCY RESULTS IN 750 STERILE COUPLES

Total number of pregnancies	293
Term pregnancies	222
Spontaneous abortions	47
Ectopic pregnancies	3
Therapeutic abortions (elsewhere)	2
Current pregnancies	19

Pregnancy occurred in 293 of the 750 wives (Table I), an over-all percentage of 39.1. There were 222 term pregnancies, including one set of twins,

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

**Present address: University of Missouri, School of Medicine, Columbia, Missouri.

47 spontaneous abortions, and 3 ectopic pregnancies. There were 19 patients pregnant at the time these statistics were compiled and 2 pregnancies were therapeutically terminated elsewhere.

Estimation of Prognosis

There are no critically established criteria by which to judge accurately the prognosis for pregnancy of any particular couple. Therefore, some general rules had to be adopted. The husband was considered to be in the poor paternity prognosis category if the seminal count was below 20,000,000 per cubic centimeter. When this was found, the data concerning the volume, motility, morphology, and endurance were usually also abnormal. The wife was thought to have a poor maternity prognosis if any or all of the following were found: (1) closed Fallopian tubes at the repeat hysterosalpingography; (2) a markedly abnormal postcoition test (when the seminal count was 20,000,000 or more); (3) an endometrial biopsy which showed a significant hypoprogestational or estrogenic effect on repeated examinations.

All husbands and wives who had none of these criteria were considered to have a good fertility prognosis. When both members of the couple had such a prognosis, the couple was assigned to the good prognosis group (Table II), and among them 240 pregnancies occurred, a pregnancy rate of 52.1 per cent.

TABLE II. PREGNANCY RESULTS AS RELATED TO PROGNOSIS

PROGNOSIS	TOTAL NO. COUPLES	PREGNANT	% PREGNANT	NONPREGNANT	% NONPREGNANT
Good	461	240	52.1	221	47.9
Poor	289	53	18.3	236	81.7
Total	750	293	39.1	457	60.9

It was found that, of the couples with either or both members in the poor prognosis group, 18.3 per cent, or 53 of 289 couples, achieved pregnancy. It was also found that it made very little difference in pregnancy results whether it was the husband, the wife, or both who were in the poor prognosis group.

As estimation of the prognosis for pregnancy was made on empiric bases, it was felt that it would be valuable to ascertain whether our criteria were valid. In order to determine this, a comparison was made of the estimated prognosis at the time of completion of the survey with other findings such as race, years of presumed sterility, primary and secondary sterility, psychosomatic estimation, and previous sterility studies. Estimated prognosis was also correlated with the length of time from completion of the survey to pregnancy and with adoption and pregnancies subsequent to adoption.

We also wanted to know whether we were justified in continuing our policy of telling each couple what we thought their chances were. A mathematical expression of this is more easily understood and helps to obviate generalizations and evasions which often constitute a major part of a physician's summary of a couple's sterility status.

Prognosis and Race.—

The large majority of our couples has come from the state of North Carolina where the white to nonwhite ratio is about 3 to 1. Among the 750 couples studied, there were only 65 nonwhite couples (Table III). The percentage of pregnancies of the nonwhite group was 13.8 (9 pregnancies) whereas the percentage of pregnancies for the white group was 41.5 per cent (284 pregnancies in 685 couples). The prognoses given to the nonwhite couples were

as follows: good prognosis, 27 couples, or 41.5 per cent; poor prognosis, 38 couples, or 58.5 per cent. These 27 nonwhite couples with good prognoses achieved 6 pregnancies, or 22.2 per cent (Table IV); the 38 nonwhite couples with a poor prognosis attained 3 pregnancies, or 7.9 per cent. The prognoses of the white couples were as follows: good prognosis, 434 couples, or 63.4 per cent; poor prognosis, 251 couples or 36.6 per cent. The 434 white couples with a good prognosis had 234 pregnancies, or 54.0 per cent; the 251 white couples with a poor prognosis achieved 50 pregnancies, or 19.9 per cent.

TABLE III. INCIDENCE OF PREGNANCY IN WHITE AND NONWHITE COUPLES WITH ESTIMATION OF PROGNOSIS

RACE	ALL COUPLES			GOOD PROGNOSIS		POOR PROGNOSIS	
	NO.	PREG.	% PREG.	NO.	%	NO.	%
White couples	685	284	41.5	434	63.4	251	36.6
Nonwhite couples	65	9	13.8	27	41.5	38	58.5
Total	750	293	39.1	461	61.5	289	38.5

TABLE IV. PREGNANCY RESULTS IN WHITE AND NONWHITE COUPLES AS RELATED TO PROGNOSIS

RACE	GOOD PROGNOSIS			POOR PROGNOSIS		
	TOTAL NO.	PREG.	% PREG.	TOTAL NO.	PREG.	% PREG.
White couples	434	234	54.0	251	50	19.9
Nonwhite couples	27	6	22.2	38	3	7.9
Total	461	240	52.1	289	53	18.3

Although the nonwhite group was not a large one, one must conclude from the large number who fell into the poor prognosis group and from the decreased incidence of pregnancy that we are dealing with a group of patients in whom there is a much higher percentage of organic disease. In most patients, pathological findings such as salpingitis and epididymitis were more extensive than those found in the white group. This was true in spite of the fact that a majority of our nonwhite patients were professional people. From our findings, one would then generally expect a much lower incidence of pregnancy in a nonwhite group of sterility patients due to an increased incidence of organic disease. It is difficult, however, to account adequately for the low pregnancy rate in the nonwhite couples with a good prognosis.

Prognosis and Years of Presumed Sterility.—

In a previous study of the first 500[1] of the 750 couples, it was found that after four years of presumed sterility, there was a significant drop in the percentage of pregnancy. In the entire group, we have attempted to find out whether this was reflected in the prognoses which were given the couples at the termination of their survey.

A period of presumed sterility of two years or less occurred in 174 couples, of whom 52.3 per cent (91 wives) became pregnant. A good prognosis was given to 120 of these couples and 62.5 per cent (75 wives) became pregnant (Table V). A poor prognosis was given to 54 couples, and 29.6 per cent (16 wives) became pregnant.

A history of two to four years of presumed sterility was given by 340 couples, of whom 40.6 per cent (138 wives) became pregnant. There were 210 couples with a good prognosis who achieved a pregnancy percentage of 53.3 (112 wives) in contrast to the 130 couples with a poor prognosis who achieved a pregnancy percentage of 20.0 (26 wives).

A period of presumed sterility of five years or more was noted in 236 couples, of whom 27.1 per cent (64 wives) reported pregnancy. There were 131 good prognosis couples in this group, of whom 40.5 per cent, or 53, achieved a pregnancy, whereas 105 poor prognosis couples obtained a pregnancy rate of 10.5 per cent (11 wives).

TABLE V. PREGNANCY RESULTS AS RELATED TO YEARS OF PRESUMED STERILITY AND PROGNOSIS

YEARS OF PRESUMED STERILITY	ALL COUPLES			GOOD PROGNOSIS COUPLES			POOR PROGNOSIS COUPLES		
	NO.	PREG.	% PREG.	NO.	PREG.	% PREG.	NO.	PREG.	% PREG.
Two or less	174	91	52.3	120	75	62.5	54	16	29.6
Two to four	340	138	40.6	210	112	53.3	130	26	20.0
Five or more	236	64	27.1	131	53	40.5	105	11	10.5
Total	750	293	39.1	461	240	52.1	289	53	18.3

After four years of presumed sterility, the incidence of pregnancy dropped well below the survey average in both the good prognosis and the poor prognosis groups. The added factor of increased age in these patients might operate to decrease fertility. We did not analyze our present data for this age factor, but in our previous report[1] the years of presumed sterility seemed more important with regard to pregnancy results than did the age of either husband or wife. It is difficult to explain, however, why the pregnancy percentage should drop from 62.5 per cent in the good prognosis couples after two years or less to 40.5 per cent after five years or more in a similar group of patients who supposedly have no serious organic pathology. Perhaps the elapsed time has eliminated those who would have become pregnant if given sufficient time and we are left with a group of patients who either have more psychosomatic problems or in whom the usual sterility studies fail to find the cause. Theoretically, this progressive drop in pregnancy results with increasing years of presumed sterility should not occur if diagnoses were always accurate and therapy were always specific. The occurrence of this progressive drop illustrates the fact that the reason for many "successes" cannot be critically documented. Certainly, one should encourage the infertile couples to seek medical advice regarding their problem before too many years of infertile mating have passed.

Prognosis as Related to Primary and Secondary Sterility.—

There is a difference of opinion regarding the import of primary sterility (no previous conceptions) and secondary sterility (previous conceptions but none within one or more years of nonprevenceptive mating). These terms are not to be confused with pregnancy wastage (sequential abortions or repeated failures to deliver a viable fetus). In order to investigate this problem further, a comparison was made of the results in couples with primary sterility as contrasted with the couples seen for secondary sterility.

TABLE VI. PREGNANCY RESULTS AS RELATED TO PRIMARY AND SECONDARY STERILITY AND PROGNOSIS

TYPE OF STERILITY	ALL COUPLES			GOOD PROGNOSIS COUPLES			POOR PROGNOSIS COUPLES		
	NO.	NO. PREG.	% PREG.	NO.	NO. PREG.	% PREG.	NO.	NO. PREG.	% PREG.
Primary	597	228	38.2	355	186	52.4	242	42	17.3
Secondary	153	65	42.5	106	54	50.9	47	11	23.4
Total	750	293	39.1	461	240	52.1	289	53	18.3

Of the 750 couples, there were 597 with primary sterility and 153 with secondary sterility (Table VI). Of those with secondary sterility, 42.5 per cent (65 wives) became pregnant, as compared with 38.2 per cent (228 wives) for the group with primary sterility. Of the 355 couples with primary sterility who had a good prognosis, 186 couples, or 52.4 per cent, achieved pregnancy; and of the 242 couples who had a poor prognosis, 42, or 17.3 per cent, attained pregnancy. In the group with secondary sterility, 50.9 per cent (54 couples) of those with a good prognosis (106 couples) had conceived, whereas 23.4 per cent (11 couples) of those with a poor prognosis (47 couples) did conceive.

Also of interest is the fact that 21 of the 597 couples with original primary sterility reported for a resurvey because of secondary sterility. Nine pregnancies (42.4 per cent) occurred in this group.

In viewing these figures we note that an almost similar percentage of pregnancy occurred in the good prognosis couples with primary and secondary sterility. A slightly higher incidence of pregnancy occurred in the poor prognosis group with secondary sterility but statistically this is a small group of patients. One does note, however, that more couples with primary sterility were in the poor prognosis group. So far as the final results were concerned, it made little difference whether the problem was primary or secondary sterility.

Prognosis and Female Psychosomatic Problems.—

Much has been said recently regarding psychosomatic factors and sterility.[2] We have grouped our female patients into three groups: those who manifested tension, anxiety, functional headaches, functional gastrointestinal symptoms, and so forth, were grouped as psychosomatically "inadequate"; those who obviously seemed able to withstand the "ordeals" in daily living and had no functional complaints were grouped as psychosomatically "adequate"; and those who did not obviously fall into either category were excluded for the purpose of the comparison.

Of the 231 wives in the "inadequate" group who had a good prognosis, 110, or 47.6 per cent, became pregnant; of the 152 wives in the "adequate" group with a good prognosis, 88, or 57.8 per cent, became pregnant (Table VII). In the poor prognosis group, 175 wives were classified as "inadequate" and 24, or 13.7 per cent, of them became pregnant, whereas among 81 wives classified as "adequate" there were 23 pregnancies, or 28.4 per cent.

TABLE VII. PREGNANCY RESULTS AS RELATED TO PSYCHOSOMATICALLY "ADEQUATE" AND "INADEQUATE" WIVES AND PROGNOSIS

PSYCHOSOMATIC EVALUATION OF WIVES	GOOD PROGNOSIS COUPLES			POOR PROGNOSIS COUPLES		
	NO.	NO. PREG.	% PREG.	NO.	NO. PREG.	% PREG.
"Adequate"	152	88	57.8	81	23	28.4
"Inadequate"	231	110	47.6	175	24	13.7
Unknown	78	42	53.8	33	6	18.2
Total	461	240	52.1	289	53	18.3

The psychosomatic estimation made was on the basis of clinical impressions which might be misleading. Comparison of the psychosomatically "adequate" and "inadequate" wives in both the good and poor prognosis groups shows a somewhat greater incidence of pregnancy in the "adequate" wives in both prognosis groups. This might be expected if psychosomatic problems are at all related to infertility. That this is not more impressive may be due to the fact that many anxieties and tensions are not obvious enough for the

clinical examiner to realize their presence or import. Trained psychologists are now assisting us in gathering more information which we hope to report at a later date.

Prognosis and Previous Sterility Studies.—

There is a general impression that one has a better chance of achieving the desired result in a "fresh" couple, who have had no previous studies, than in a couple who have been previously studied without results. In order to investigate this thesis more closely, a comparison was made between those patients who had had previous studies and those who had not, in both the good and poor prognosis groups.

Previous sterility studies, usually incomplete, had been done elsewhere on 50.1 per cent (376 couples) of the 750 couples. There were 147 pregnancies (39.1 per cent) in this group. Previous studies were done in 54.9 per cent (253 couples) of the 461 couples with a good prognosis. Pregnancy occurred in 49.8 per cent (126). No previous studies were done on 208 couples with a good prognosis and 114, or 54.8 per cent, of the wives became pregnant. In the 289 couples with a poor prognosis, 123, or 42.6 per cent, had had previous studies, and 21 of these couples, or 17.1 per cent, achieved pregnancy. Among the 166 with a poor prognosis who had no previous studies made, 32, or 19.3 per cent, became pregnant (Table VIII).

TABLE VIII. PREGNANCY RESULTS AS RELATED TO PREVIOUS STERILITY STUDIES AND PROGNOSIS

PREVIOUS STUDIES	ALL COUPLES			GOOD PROGNOSIS			POOR PROGNOSIS		
	NO.	PREG.	% PREG.	NO.	PREG.	% PREG.	NO.	PREG.	% PREG.
Done	376	147	39.1	253	126	49.8	123	21	17.1
Not done	374	146	39.0	208	114	54.8	166	32	19.3
Total	750	293	39.1	461	240	52.1	289	53	18.3

There was a slight difference noted between the couples who had previous studies and those who had not in the good prognosis group and very little difference in the pregnancy results in the poor groups. Strangely enough, fewer previous studies had been done in the poor prognosis group of patients. It is quite probable that many couples who are given a poor prognosis on the basis of a previous survey do not seek further medical advice.

Prognosis and Time From Survey to Pregnancy.—

A comparison was made of the time required for a pregnancy to occur after the estimated prognosis. Of the 240 couples with a good prognosis who initiated a pregnancy, 79.2 per cent (190 couples) did so during or within six months after the survey. At the end of twelve months, 87.5 per cent (210 couples) had achieved pregnancy, and 92.5 per cent (222 couples) did so within 24 months of completion of the survey. The results in the 53 couples with a poor prognosis who conceived were as follows: only 49.0 per cent (26 wives) were pregnant after six months; at the end of twelve months, 71.7 per cent (38 wives) were pregnant; and after 24 months, 46 wives, or 87.0 per cent, had become pregnant (Table IX).

TABLE IX. TIME FROM SURVEY TO PREGNANCY AS RELATED TO PROGNOSIS

TIME FROM SURVEY TO PREGNANCY	ALL COUPLES (293)		GOOD PROGNOSIS (240)		POOR PROGNOSIS (53)	
	NO.	%	NO.	%	NO.	%
During or first 6 months	216	73.7	190	79.2	26	49.0
First 12 months	248	84.6	210	87.5	38	71.7
First 24 months	268	91.5	222	92.5	46	87.0

These data support our original contention in considering the good prognosis couples. One would expect the results achieved in the poor prognosis group to take longer as most of these couples required definitive treatment of either the husband or wife or both before pregnancy ensued. It is interesting to note, however, that at the end of two years, the percentage of couples who had achieved a pregnancy was about the same in the patients of the two groups (good and poor prognosis couples) who eventually became pregnant.

This information is of value when the couples ask how long they should wait before considering adoption. They can be told that 87.5 per cent of the pregnancies in the good prognosis group and 71.1 per cent of pregnancies in the poor prognosis group occur within a year of completion of the survey. They are thus usually advised to wait a year before considering adoption.

Prognosis and Adoption With Subsequent Pregnancy.—

It has been commonly accepted that there was more than a casual correlation between adoption and subsequent pregnancy in presumedly infertile couples. The only significant documented evidence to the contrary seems to be that by Hansen and Rock[3] who report no such correlation in a questionnaire-sampled study of adopters in the state of Massachusetts. Of our 750 couples, 74 adopted children following the survey. Of these, 13, or 17.6 per cent, became pregnant following adoption of a child. The prognosis given these couples who later adopted was as follows: good prognosis, 46 couples, with 12 pregnancies (26.1 per cent); poor prognosis, 28 couples, one pregnancy (3.6 per cent) (Table X).

TABLE X. ADOPTION WITH SUBSEQUENT PREGNANCY AS RELATED TO PROGNOSIS

PROGNOSIS OF COUPLES	TOTAL NO. COUPLES	ADOPTIONS		PREGNANCIES AFTER ADOPTION	
		NO.	% ADOPTING	NO.	%
Good	461	46	10.0	12	26.1
Poor	289	28	9.7	1	3.6
Total	750	74	9.9	13	17.6

Those couples who adopted were in two categories, good prognosis couples who had not achieved a pregnancy in a year or more (usually longer) after completion of their survey, and poor prognosis couples whose outlook for pregnancy was unusually poor. In the latter group one would scarcely expect pregnancy to follow adoption. In the former group, one would have expected the incidence of pregnancy to be higher than it was if adoption were a "trigger" mechanism. However, most of these pregnancies occurred within six months of the time of adoption, which suggests a psychosomatic influence.

Summary

Seven hundred and fifty sterility *couples* were completely studied. It should be emphasized that this is a study of 750 *couples*. It does not include the studies made on women patients in our clinic who were seen for repeated abortions, hysterograms, or isolated diagnostic studies. Pregnancy occurred in 293 (39.1 per cent) of the 750 wives. An estimated prognosis, dependent on survey findings, was given the couples at completion of the survey. The couples were divided into two groups: those with a good fertility prognosis and those with a poor prognosis. The criteria by which prognosis was estimated are given. There were 461 couples in the good prognosis group and 240 couples (52.1 per cent) conceived. There were 289 couples assigned a poor prognosis, and 53 couples (18.3 per cent) conceived.

Estimated prognoses at completion of the survey were compared with other findings as follows:

1. White and nonwhite couples were contrasted. More nonwhite couples had a poor prognosis due to increased organic pathology. However, even in the couples with a good prognosis, the percentage of pregnancy in the nonwhite was considerably lower than in the white.

2. Increased years of presumed sterility reduced the incidence of pregnancy in both good and poor prognosis couples.

3. Whether the problem was one of primary or secondary sterility made little difference in the final results obtained.

4. The 750 wives were psychosomatically evaluated using certain available criteria. There was a slightly higher incidence of pregnancy in wives who were felt to be psychosomatically "adequate."

5. Previous sterility studies had very little effect on the incidence of pregnancy.

6. It was found that couples with a poor prognosis were slower in achieving a pregnancy than were couples with a good prognosis.

7. The number of pregnancies following adoption was not so high as might be expected if adoption were as good a "trigger" mechanism as is popularly supposed.

References

1. Turner, V. H., Davis, C. D., Zanartu, J., and Hamblen, E. C.: South. M. J. **44**: 628, 1951.
2. Turner, V. H., and Davis, C. D.: Presented at the First World Congress on Fertility and Sterility, New York City, N. Y., May 24-30, 1953.
3. Hanson, F. M., and Rock, J.: AM. J. OBST. & GYNEC. **59**: 311, 1950.

Discussion

DR. WILLIAM DURWOOD SUGGS, Richmond, Va.—Drs. Turner, Davis, and Carter's paper is important from two standpoints. First, a procedure is outlined for the investigation and treatment of sterility which has succeeded in 39.1 per cent of a large series of couples completely studied. Second, criteria are suggested as a result of their findings and results which seem to establish some basis for prognosis. That these criteria are of prognostic significance is shown by the fact that the rate of conception is approximately three times as great in those placed in the "good prognosis" category as in those given a "poor prognosis." However, the fact that conception occurred in 18 per cent of the poor prognosis group suggests that perhaps these criteria are too strict and the entire series might be further broken down into smaller groups of good, fair, and poor prognosis.

Dr. Turner does not go into detail regarding therapy or length of treatment. Although one cannot be critical of the type of management which procured conception in 39.1 per cent of cases, we have felt that seeing these patients at monthly intervals for review and encouragement for at least a year, or until conception takes place, definitely improves the chances for conception. This is particularly true in those with impaired fertility.

The degree of cooperation on the part of both husband and wife is an important factor in prognosis. We classified cooperation as excellent in only 18 per cent of our cases, good in 45 per cent, and poor in 30 per cent. Lack of cooperation is unintentional in many instances and can be improved by monthly conferences. The survey and treatment are incomplete in 68 per cent of our cases.

The fact that conception followed adoption in 26 per cent of the good prognosis group strongly suggests a psychosomatic element, as is brought out by Dr. Turner. Inasmuch as psychosomatic factors often regress spontaneously or are amenable to therapy, one might advise against adoption for at least two years or longer, depending upon the duration of sterility, age, and other factors.

Spontaneous abortion occurred in 16 per cent of the cases in this series which is in line with the estimated incidence for the population at large. Our experience has been that abortion rarely occurs in patients treated for sterility. We have attributed this to the fact that factors detrimental to conception have been corrected or improved and also because the patient comes under observation very early in pregnancy, permitting prophylactic measures and advice to be given.

We feel that homologous therapeutic insemination has a definite place in the poor prognosis group and freely employ it when anatomical or developmental defects in either husband or wife mitigate against normal insemination of the cervix; when the seminal specimen is deficient in volume; and in the presence of oligospermia.

One must be prudent in discussing prognosis with couples of relative, but not absolute, infertility since they are often prone, when given a poor prognosis, to assume that conception is impossible. Correlation of data, as in this study, offers a basis for rendering an opinion in terms of easily understood mathematical probability.

DR. ARTHUR J. WALLACE, JR., Tampa, Fla.—The thing that impresses me most about this paper is the relatively low percentage of success achieved in the good prognosis group. It certainly brings to our mind that there are many factors involved in infertility that have not been answered by the profession to date. There is roughly only a 50 per cent success in the group for which no cause for sterility could be found.

Our study of infertile couples is not so complete as that carried out by the group that presented this paper. The major difficulty is getting the cooperation of both husband and wife. By and large, we have to be satisfied with those procedures that give us the greatest amount of help in arriving at a correct conclusion, and at the same time keep the expense and the number of visits to a minimum. As a result, we have to make a compromise on certain issues.

We have found the Rubin test using carbon dioxide gas rather than radiopaque media highly satisfactory in determining the patency of the tubes, and we feel that the ease of performing this examination and the saving in the expense of the procedure make it in our hands more suitable than the routine use of hysterosalpingography. The latter examination is used in those patients who have tubal obstruction as determined by the Rubin test, or where the insufflation for one reason or another cannot be carried out satisfactorily.

The basal body temperature in a rather high percentage of patients gives us the same information as the endometrial biopsy, and we find that giving the wife this little task to perform is a good way to keep her pacified while we are awaiting the cooperation of the husband in having semen analysis and urological examination. Semen analysis is carried out by a urologist and it is our practice to await the results of this examination before the insufflation study. In the case of a completely nonfertile husband, the Rubin test is not performed. For the past three years, 25 per cent of the husbands failed to have the urological examination.

There is no mention in this paper of the lowly pessary as a mechanical aid in overcoming sterility. We have seen on several occasions the correction of a third-degree retroversion result in pregnancy. The use of a properly fitted Hodge-type pessary maintains the correct position of the corpus so that the direction of the cervix is changed from behind the symphysis to the posterior fornix of the vagina making the cervical canal more approachable by the sperm.

We have not found artificial insemination using the husband's semen of any real value except in those cases of uncorrectible retroversion or recurrent cervical stenosis.

DR. TURNER (Closing).—Dr. Wallace mentioned using the Rubin test. We do not use this as a routine because at least 50 per cent of our patients have had previous surveys elsewhere and we feel that exact diagnosis is important. We do a combined type of examination, using both gas and oil under fluoroscopic control and roentgenograms as needed.

We have not found that the basal body temperature replaces the endometrial biopsy. We studied this matter and found that many patients with apparently normal temperature curves would have severe degrees of hypoprogestational endometrium and even on one or two occasions estrogenic endometrial patterns. The majority of patients with a normal temperature curve will have a progestational endometrium, but this is not always true, and I have even suspected many patients of sending in charts with variations without actually taking their temperatures. We have also found patients who reported exactly the same temperature every day for as long as 10 or 12 days, and anyone who has experience with basal body temperatures knows that this is very unlikely if they are taken accurately.

There is no mention of treatment in this paper because primarily it was not a paper on treatment, but a paper on correlations and results.

PATHWAYS OF MEDICINE, REFLECTIONS OF A CONSERVATIVE PHYSICIAN*

EDWARD A. SCHUMANN, M.D.,** PHILADELPHIA, PA.

FIFTY-FOUR years ago I graduated from a prominent medical school in the East and enjoyed internship in one of the great hospitals of the country. Incidentally, there were no residencies available at this time and upon completing internship one learned a specialty the hard way: the retractor-holding way, you know. Medicine at that time was considered to be on a very high plane and the profession applauded itself for the vast advances which had been made.

Surgery, as you know, was well developed, although operations then considered very major would be noted as somewhat trivial today. Cholecystostomy was the rule, no cholecystectomies being performed. Gastroenterostomy was just beginning to emerge as a very formidable procedure in the management of gastric ulcer. Radical gastric resection was practically unknown. Anesthesia was well developed, though we had only the open-drop ether and chloroform and occasionally a little nitrous oxide. Spinal anesthesia, cocaine or its derivatives were practically unknown.

The roentgen ray had passed through the stage when one delineated coins in a purse, or looked at the skeletons of mice as a matter of interest. And the roentgen ray was beginning to be utilized as a means of diagnosing fractures of the long bones. Visceral studies were entirely in the future and it is an interesting commentary that in association with Dr. George E. Pfahler, who later became one of the most distinguished roentgenologists in the world, I was able to assist in some experiments attempting to localize brain tumors. We took fibroid nodules from the autopsy room and implanted them in the brains of cadavers and then attempted to localize them by roentgenological visualization, totally without success, of course. It was not until years later that the improvement in apparatus and the increase in power made the present high degree of roentgen diagnosis possible.

Neurosurgery was in its infancy and surgery of the heart and chest had not been attempted, to the best of my knowledge. Blood transfusions, parenteral therapeutics of all sorts, were unknown. Here again it was my privilege to be present at one of the very early blood transfusions in Philadelphia when a surgical colleague placed the donor and recipient side by side, dissected out and anastomosed the median basalic veins of both, and permitted blood to flow from the donor into the recipient for a variable period of time. When it was estimated enough had been received the anastomosis was taken down and the veins again repaired. This, of course, was followed very shortly by a syringe method when all sorts of ingenious automatic syringes were made for blood transfusions, only to be replaced much later by our present methods. We had no means of combating shock except the Murphy drip which was instituted during my intern years and was considered of

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

**Guest speaker.

enormous value, which it was. Hypodermoclysis was known, but no intravenous therapy whatsoever. Of course the endocrines and antibiotics have come in your time.

Gynecology had come fully armed and prepared to take care of all the ills affecting womankind, and was an advanced specialty from its very beginning. The operations of gynecology were manifold and every woman presenting the slightest evidence of pelvic illness was immediately subjected to some form of operation or other. You will note, curiously enough, that of all the specialties gynecology has advanced least in technique. Refinements have taken place, it is true, but no new major procedures other than the evisceration operations for malignancy now being performed and evaluated have taken place in the past fifty years. One might mention the Manchester operation, the Sturmdorf trachelorrhaphy, and practically nothing else. The Wertheim operation was very popular and was just as radical as it is today except that lymph node dissection was not carried out. The mortality of this procedure was very high and for very good reason. First, there was no means of combating shock other than strychnine and heat, and hot coffee enemas. That was all we knew for shock. Second, there was no method of treating carcinoma of the cervix except radical operation or morphia. Therefore, many women elected and insisted upon an attempted operation in cases which would now be considered entirely inoperable. The fact that our anesthetic methods were so imperfect and crude, partly explains why the mortality of Wertheim operations was so high.

When, in 1904 or 1905, Pfannenstiel visited the United States and was a guest at a hospital at which I was a junior assistant, I, because of my knowledge of German, was assigned to assist him in the performance of a Wertheim operation. He did this procedure with his accustomed skill and care and pointed out to me with great emphasis a tiny vessel which arose from the ureter and ran down into the parametrium. "This vessel," said he, "you must preserve if you would avoid sloughing of the ureter." It has been with great pleasure that I learn of the rediscovery of this ureteral vessel just two or three years ago.

If you will examine the instrument cabinets in your hospital you will find, strangely enough, that all the instruments used in your gynecological surgery, with the exception of some electrically lighted diagnostic devices, bear the names of operators long since gathered to their fathers. You will see Kelly clamps; you will see Péan hemostats; you will see Pozzi clamps, all ancient instruments, from the standpoint of modern medicine. So, I repeat, it is a curious fact that operative gynecology has not advanced greatly because it reached its acme, so far as is foreseeable, many years ago. It is true that complete hysterectomy was not generally performed except in the presence of malignancy. Supravaginal hysterectomy was the operation of choice. I am told that vaginal hysterectomy is a comparatively new procedure. Its popularity is new, but anyone who saw Pryor, of New York, do his vaginal hysterectomies many, many years ago will realize that the operation was well established long since.

In obstetrics the picture was entirely different, and the modern young obstetrician can hardly visualize the conditions which attended the special practice of obstetrics. The pregnant woman visiting her obstetrician for the first time underwent a more or less cursory physical examination. The diagnosis of pregnancy was confirmed by manual examination. The pelvis was measured with a pelvimeter and manually. A specimen of urine was examined and the patient then advised to inform the obstetrician immediately upon the occurrence of undue bleeding, much edema of the legs and particularly of the face, severe and continuous headache, or the occurrence of labor as evidenced by rupture of the membranes or a little bleeding or irregular pains. Under the

stimulus of any such symptoms the obstetrician was to be notified when he would then attend the patient. She did not see her obstetrician again until he was called to attend the delivery. Prenatal care as we know it was nonexistent. There were no blood studies; there were no weight estimations; there were no blood pressure investigations, because, as a matter of fact, the sphygmomanometer was invented during my student days, and even in my internship there was tremendous controversy as to the meaning of the various degrees of hyper- and hypotension. It was an entity not understood in medicine. That was the situation in our specialty fifty years ago.

As to the situation today, I will not attempt to go into any discussion. You know it far better than I. But it is true that in all phases of human endeavor progress is continuous but irregular, irregular in amplitude and irregular in rate.

At various unpredictable periods there come great summits of achievement which alter the entire conception of medicine. Thus, for example, in the past fifty years we have four such epochs: the discovery of the roentgen ray and radium, the use of blood transfusion and parenteral therapeusis in general, the discovery of the endocrines, and, of course, the antibiotic drugs. It is from these peaks of achievement that we are at present engaged in conducting our attack upon disease. It should be noted, however, that these advances of the past fifty years, while epochal, are not revolutionary, unless possibly one excepts the x-ray. They have not materially changed the practice of medicine. They have only added vastly to our armamentarium.

If now you will turn to the fifty years preceding this, from 1850 to 1900, we note that two events occurred in a rather close time relationship which entirely changed the picture of medicine, which made modern medicine possible, particularly from a surgical aspect. I refer, of course, to the discovery of anesthesia and of bacteriology with its by-product of asepsis. Without these two discoveries no modern medicine could be conceived under any circumstances whatsoever. So here we have a tremendous change occurring in the preceding half century which, as I have said, has altered the whole picture. Before this time, curiously enough, there was no marked advance made in medicine with the single exception of the smallpox vaccine since Ambroise Paré invented the ligature in the sixteenth century.

But in spite of all these achievements something has been lost. The spiritual relationship between the physician and patient in which the emotional and the psychic problems of the patients were presented to the father confessor-physician, who solved and mitigated these difficulties by his knowledge of human nature and of his particular patient, is long gone. It is in recognition of this fact that the great crusade for the re-emergence of the general practitioner took place just a few years ago. But that, I note, has not worked out just as intended. The young general practitioner is educated just as well as the rest of his classmates and he, finding a patient with any obscure condition appealing to him, at once rushes her off, or him off, to x-ray examinations, to multiple laboratory tests and the like, possibly to a psychoanalyst, and finding the condition still obscure, immediately refers the patient to some specialist or other. So that the general practitioner relationship, except possibly in sparsely settled districts, has not developed as we thought it would.

Another thing in this relationship: When a patient enters one of the great clinics in the country curious things happen. At first the patient is received and a careful and most meticulous history taken by a team of physicians. Then he or she is passed to the diagnostic team which orders all of the laboratory tests, the x-ray work, and so on, all of which is done in perfect detail. Then the patient finally, a diagnosis having been made, comes to the operative

team where she is operated on with great care and skill. The operation being completed she goes to the postoperative team who look after her postoperatively also with the greatest care and skill, so that finally our patient is discharged from the clinic, her lesions having been removed, her illness alleviated beyond criticism, and then a psychiatrist is necessary to solve the emotional problems and the frustations and fears with which she has been beset in the clinic.

Another loss, as I conceive it, has been the decay of physical diagnoses in observation of the patient. Now it is perfectly true that a fluoroscopic examination of the chest is more revealing than auscultation and percussion and that a cholecystograph will offer a more accurate picture of gall bladder disease than palpation and history. But, nevertheless, I believe that the art of physical diagnosis still is of value and I believe particularly that observation of the patient is of great value. Our older confreres gained much knowledge by close observation of the ill patient and such things are still attributes to be reckoned with.

To sum up one man's view of our specialists, I think it may be said that obstetrics has passed through the phase of midwifery in which the man physician was not permitted to enter the lying-in room. It has passed through the phase lasting about one hundred years of our being a surgical specialty and now the wheel is turning full circle and obstetrics is again becoming a midwifery problem, the midwife, in this instance, being the highly trained obstetrician who exercises the greatest care in the supervision of the physiological and pathological processes concerned with pregnancy and labor.

I believe that we must, in the future in medicine, give up in a large measure the problem of curing disease and devote ourselves mainly to the problem of prevention of disease. We could take excellent examples from internal medicine. You know there are many diseases very prominent in the past which have become almost extinct, and which are extinct in all communities where adequate prevention and control are available. Typhoid fever, smallpox, typhus, cholera are all extinct diseases. Measles, whooping cough, scarlet fever are rapidly joining these ranks, and if our modern vaccines prove as valuable as we hope poliomyelitis will join this group of forgotten illnesses.

It has been said by wise men that surgery is inevitably a confession of defeat unless it is practiced in the relief of trauma. In gynecology we are still entirely too surgically minded. We cure disease rather than attempt to prevent it. The tremendous amount of study devoted to the cause of cancer, now going on, will inevitably bear fruit one day, and when the cause of cancer has been discovered, prevention and prophylaxis will rapidly become automatic, thus relieving gynecology of much of its surgery.

In the benign diseases more work has to be done. Recent studies with very large doses of estrogen seem to show some relationship between this hormone and the production of fibroid tumors, myomas. It may well be that further studies will disclose the causal relationship of the endocrines to myomas, and a method of prevention of the formation of these tumors may develop. The same is true of ovarian cysts with the exclusion of teratomas, which will probably always require surgery.

Pelvic inflammatory disease as we knew it in my youth has practically been eliminated, at least in Philadelphia. The prophylactic use of the antibiotics in cases of abortion, the education of the public to seek penicillin at the first symptom of gonorrhea have resulted in an enormous diminution of pelvic inflammatory disease, and further diminution is to be expected.

With regard to endometriosis, little progress has been made, but again a further evaluation of the relation of endocrines to the development of endometriosis will, I think, result in methods for its prevention.

Functional uterine bleeding can in most instances be prevented by proper nutrition and I am quite sure that here again further endocrine studies will be of value.

I believe that it may be said then that should the gynecologist devote himself with great assiduity to the prevention of the occurrence of lesions of the pelvic organs his work will be crowned with success in the future, and gynecologists of the future will find themselves to be a combination of endocrinologist, nutritionist, and psychiatrist. To paraphrase an old doggerel:

The operators are dust,
Their good knives are rust,
Their souls are with the saints we trust.

SURGICAL EMERGENCIES IN PREGNANCY AND IN THE PUERPERIUM*

WILLIAMS M. BRYAN, JR., M.D., COLUMBIA, S. C.

(From the Department of Obstetrics and Gynecology, Columbia General Hospital)

ADMITTEDLY this is a subject too vast to cover amply in the short time allotted. The subject matter herein discussed should call forth both agreements and the expression of prejudices. If so, then the presentation of this paper may be justified.

The more commonly seen placental accidents and surgery for cephalopelvic disproportion will be omitted. To be discussed will be appendicitis, myomas, ovarian tumors, intestinal obstruction, and vascular accidents including venous hematomas and cerebrovascular accidents.

Appendicitis

In a collected review in the literature of 94,599 pregnancies there were 93 cases of operative appendicitis or an incidence of 1 in 1,017 patients. Meharg and Loop[1] cite an operative incidence of 1 in 244 cases.

The data that we collected in the twenty-four months from January, 1952, through December, 1953, in the five hundred bed Columbia General Hospital showed an incidence of 13 cases in 4,618 pregnancies or 1 in 355 (Table I).

TABLE I. STATISTICAL DATA ON CASES OF OPERATIVE APPENDICITIS IN PREGNANCY, JANUARY, 1952, THROUGH DECEMBER, 1953

Number of cases	13 in 4,618 pregnancies or a frequency of 1:355
Incidence of operative appendicitis in pregnancy collected from the literature	93:94,599, or 1:1,017
Age of patient	18-42 years (84.6% 22-32 years)
Days hospitalized	3-12 (84.6% 4-11 days)
Chemotherapy administered	8 out of 13 patients
Morbidity	None
Miscarriages	1 (5 weeks postoperative)
Condition on dismissal	Normal in 13 cases
Type of incision	McBurney, 9 cases; low midline, 3 cases; right lower quadrant transverse, 1 case

By the end of the sixth month of gestation the appendix becomes an abdominal organ and displacement is lateral and cephalic removing the point of maximal tenderness away from the typical McBurney's area.[2]

Early diagnosis is important and a careful history is imperative since it may become of greater significance than the physical signs, especially if the latter are nonlocalized. Characteristically the pain begins in the epigastrium preceded by a period of anorexia. The pain may persist here for eight or more hours and be accompanied by an urge to defecate as stressed by Keyes.[3]

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

Constipation is much more common than diarrhea and the popular use of various cathartics in the obstipated pregnant patient is fraught with danger even in the face of vague abdominal signs and symptoms.

As inflammation increases, the pain shifts to the right lower quadrant with rebound tenderness referred to this area. Pressure on the pregnant uterus from the left side will often elicit pain in the right lower or middle quadrants. A vaginal examination at this point will help differentiate appendiceal from pelvic inflammatory disease. Signs and symptoms may be masked if antibiotic agents are given before a reasonable diagnosis is made. The injudicious use of these drugs may allow a period of dangerous calm to prevail, with subsequent rupture of the appendix and its attendant increased morbidity and mortality.

The postpartum patient with acute appendicitis poses a particularly perplexing diagnostic problem because of the so-called afterbirth pains that may occur normally or that may be increased by the use of routine oxytocic drugs. Analeptic medication given post partum may also veil important physical signs so helpful in a correct diagnosis of acute appendicitis. It may be said, parenthetically but not facetiously, that the worse time a woman can choose to have appendicitis is while being a patient in a maternity ward, especially after delivery.

Laboratory and x-ray studies aid in corroborating the diagnosis but may be deceptive if used solely as the deciding factor governing the choice to operate. A known leukocytosis occurs in pregnancy, whereas the white blood count in a case of gangrenous appendicitis may be depressed, as pointed out in a case in our series. A catheterized urine specimen showing leukocytes and erythrocytes may help to diagnose a pyelonephritis which is so often the cause of signs and symptoms mimicking appendicitis, whereas radiologic evidence of a ureteral stone may pin-point the cause of right lower quadrant pain otherwise erroneously called appendicitis.

Krieg[4] discussed two hundred cases of appendicitis during pregnancy collected from four large Detroit hospitals. The maternal mortality rate of 2 per cent could probably have been reduced to zero according to the author who considered the history of the case as the most reliable feature in the diagnosis.

The incidence of normal appendices in our series was 41.6 per cent, yet this relatively high incidence need not be scoffed at for, in the words of Douglas,[5] "The experience of many indicates that prompt surgical intervention in the early months of pregnancy results in insignificant maternal morbidity and abortion incidences. Improved results then can be produced by extending early operation to those patients manifesting signs of appendicitis in the last trimester of pregnancy. If a policy of earlier and more frequent operation is adopted for what may seem at the time relatively benign symptoms and signs, it may be anticipated that a certain number of patients will be operated on needlessly. In view of the insignificant risk involved it is apparent that this is a small price to pay compared to the tragedy following procrastination and subsequent rupture."

Prior to term the surgical treatment of acute appendicitis is fairly well agreed upon. A properly placed McBurney muscle-splitting incision is made and the appendix is removed. At term the surgical treatment varies according to different authors and clinics.

Myomas

The need for surgical intervention in fibromyomas during pregnancy and in the puerperium, which incidence approximates 1 per cent, is fortunately

very uncommon. Operation is indicated if there is tumor impaction or if the myoma in any way interferes with descent of the presenting part. The twisting of a pedunculated subserous myoma or any gangrenous change necessitates laparotomy. The question of whether red degeneration of a myoma calls for operative interference is still debatable.

The significance of myomas of the uterus during pregnancy is great because of the attendant complications so frequently seen, which are recognized as an increased incidence of puerperal morbidity and dystocia as well as a higher percentage of abortions, premature labors, and abnormal presentations. There is a higher incidence of these tumors in elderly primigravidas.

Of 445 complicating fibromyomas in pregnancy collected by Grandin[7] at the Sloane Hospital for Women, 44, or 10 per cent, of the patients were operated upon in the antepartum course. Many factors govern the decision to operate on a myoma during pregnancy. The position as well as the site of the tumor is of great importance because of the changes that may occur during pregnancy and render operation unnecessary. Pedunculated tumors should be watched carefully for signs of twisting, degeneration, or rupture. Low cervical myomas may seem to offer an obstruction to labor during the antenatal period but may subsequently grow out of the pelvis and allow delivery per vaginam. Submucous myomas may be completely unnoticed until after delivery, at which time fever, pain, and infection may precede the expelling of the tumor, thus proving its presence. Three such cases were reported by Gainey and Keeler.[8]

In certain instances changes within a tumor during pregnancy may initiate a pathologic process that causes pain, fever, leukocytosis, and an increased sedimentation rate. The decision to treat medically or to operate may be difficult. Red degeneration of a myoma is an example of such a case.

Throughout the literature may be found case reports of red-degenerated tumors removed during pregnancy with an oftentime favorable outcome. Red degeneration is a hemorrhagic infarction of a previously hyalinized myoma.[10] Conservative management has been stressed by many including Beck,[11] Titus,[12] Douglas,[5] Greenhill,[13] and Philpott.[14] Johnston[15] handled 10 cases of degenerated myomas during pregnancy conservatively, but added a word of caution concerning omentum adherent to the degenerated tumors, claiming that pressure on these myomas may tear the omentum, resulting in serious intraperitoneal bleeding.

If a tumor twists, becomes impacted or necrotic, operation is a necessity. But what approach should be made if a large, broad-based intramural or subserous tumor undergoes red degeneration with accompanying pain, fever, and leukocytosis? Stated differently, what may be expected if the decision is made not to operate in the face of these signs and symptoms?

Case History.—Mrs. P. H., a 24-year-old white gravida i, para 0, had her last menstrual period on April 24, 1953, and had an estimated date of confinement of Feb. 1, 1954. At a prenatal examination at three months of gestation, a small myoma was palpated on the lower uterine segment.

At approximately five months' gestation the patient was hospitalized because of epigastric and right lower quadrant pain of two days' duration. The physical examination was noncontributory except for pain and tenderness localized in the right lower quadrant between the anterior iliac spine and the umbilicus. Oblique and anteroposterior radiologic projections showed evidence of a single fetal skeleton and an ovarian or uterine tumor.

Because of persistent abdominal pain, a rising leukocytosis, and a sedimentation rate increased above the normal pregnancy rate, a laparotomy was done and a 25 cm. myoma was enucleated from the right side of the corpus uteri without invasion of the endometrial cavity. The pathologic diagnosis was leiomyoma showing red degeneration.

Six weeks postoperatively the patient went into labor and delivered premature twins, a boy and a girl. The former died after twelve hours. The girl weighed 1 pound and 11 ounces on the tenth day of life and weighed 4 pounds and 15 ounces on dismissal three and one-half months later. At the age of 3 months there was evidence of retrolental fibroplasia.

Ovarian Tumors

In the first trimester of pregnancy the finding of an ovarian tumor should be accompanied by frequent examinations to determine the size and consistency of the tumor and its changes under palpation. Cysts over 10 cm. in size should be removed, but most smaller physiologic cysts in the younger woman frequently change in size in a few months' period of observation and rarely exceed 10 cm., except possibly the theca-lutein cysts.

During the childbearing age most ovarian tumors are simple follicular or corpus luteum cysts and indiscriminate removal may result in abortion. Larger serous cystomas also may be watched during the early interval of gestation. The problem of treatment becomes more acute if the differential diagnosis suggests tubal pregnancy with hematocele or torsion of the cyst.

Careful pelvic examination after emptying the bladder and rectum may help to resolve an otherwise difficult diagnosis. Many lesions of nonovarian origin may mimic a tumor of the ovary. Intraligamentous or parovarian cysts are quite difficult to diagnose preoperatively and one may be readily confused by an appendiceal abscess, a redundant sigmoid, a low-lying cecum, a myoma of the round ligament, a pelvic kidney, a bicornuate uterus, or certain colon diseases.

If operation is imperative in the first trimester because of torsion, hemorrhage, or suppuration, abortion need not be considered inevitable, for corpora lutea have been removed from gestations as early as eight weeks with a successful termination of pregnancy. Operation is best deferred until after the third month, thus allowing placental function to continue the hormonal control of pregnancy. A point of operative procedure in the case of a twisted cyst that may be re-emphasized is the need to suture or clamp the base of the pedicle prior to untwisting the cyst to avoid the possibility of embolism.

In the second trimester diagnosis becomes more difficult because of the enlarging uterus and displacement of the ovarian tumor although it may arise out of the pelvis and offer no serious impediment to delivery.

Solid or bilateral tumors should be promptly inspected since the occurrence of dermoids is not infrequent during pregnancy and, should bilateral ovarian dermoids be found, especially in the younger gravida, every effort should be made to conserve ovarian tissue, a fairly simple task, since in this type of tumor ovarian tissue is distinct from the neoplasm.

Should an operable ovarian cyst be found in the third trimester of pregnancy its removal should be deferred until the late puerperium if possible. In the elderly primigravida removal of the tumor may accompany elective cesarean section.

Case History.—Mrs. F. K., a 21-year-old white gravida i, para 0, abortions 0, had her last menstrual period Nov. 1, 1950, with the estimated date of confinement Aug. 8, 1951.

From Jan. 1 to 5, 1951, the patient noted a brownish vaginal discharge. She was admitted to the hospital on Jan. 17, 1951, because of pain in the left lower quadrant accompanied by some vaginal spotting.

A pelvic examination showed a small, bluish, and slightly softened cervix. In the left adnexa was a soft, tender mass about 10 cm. in diameter. The uterus was slightly larger than normal. The frog test was positive.

Because of increased pain and the possibility of a tubal pregnancy with hematocele despite normal laboratory findings, a laparotomy was done. A left ovarian cyst the size of a small grapefruit was found attached to the broad ligament by a 7 cm. pedicle. The cyst was removed in toto and opened, allowing 200 c.c. of straw-colored fluid to escape. The pathologic diagnosis was cortical fibrosis of the ovary with large corpus luteum cyst. The postoperative course was smooth and the patient was delivered of a living male infant on Aug. 30, 1951, without complications.

Intestinal Obstruction

Intestinal obstruction is infrequently seen during pregnancy and in the puerperium. Because it is so often not diagnosed early and treatment is delayed, and because its attendant maternal and fetal mortality is so high, it warrants frequent reiteration.

At the Margaret Hague Maternity Hospital there were 6 maternal deaths due to intestinal obstruction during pregnancy from 1931 through 1949.[16] Waters and McCaw[17] stated that intestinal obstruction complicating pregnancy is a life-threatening but relatively neglected condition. In a discussion by these authors of 6 fatalities from obstruction, they mentioned the pitfalls of diagnosis and the preventability of death.

An abdominal operative scar in the presence of colicky pain constitutes a situation in which intestinal obstruction is to be ruled out. Negative x-rays create a false sense of security and should be repeated if doubtful. Foul-smelling vomitus is partly diagnostic and laboratory evidence of a fall in blood chlorides, alkalosis, and dehydration corroborates the clinical picture. Fever and an increased pulse rate indicate an electrolyte imbalance and the beginning of a degenerating bowel. A surgical consultation is imperative.

Quite possibly a properly functioning Miller-Abbott tube can decompress an inflated bowel and obviate surgery but progressive signs and symptoms of unreleased obstruction warrant early operative interference while the patient is still in good physical condition. The threat of miscarriage should remain secondary to the release of the obstruction. Electrolytes, plasma, antibiotics, and whole blood if there is evidence of anemia should be minimum prerequisites to surgery. Enterostomy is best left to the discretion of the surgical consultant.

Case History.—Mrs. D. J., a 22-year-old white gravida ii, para 0, abortions i, had her last menstrual period Feb. 27, 1950. The estimated date of confinement was Dec. 4, 1950.

The patient first noted pain and tenderness in the right lower quadrant the evening prior to admission to the hospital on Oct. 29, 1950. The pain was cramping in nature and increased in severity. A general examination was normal except for abdominal evidence of muscle guarding and marked tenderness in the right lower quadrant over the site of a previous McBurney's scar. Rebound tenderness was referred to the right lower quadrant, occasional peristaltic rushes were heard, as were nomal fetal heart tones in the uterus that measured 18 to 20 cm.

X-ray findings: There was a large amount of gas in the lower bowel surrounding an enlarged uterus. This had the appearance of gas in the colon which is not unusual in this stage of pregnancy. There was no definite evidence of obstruction. Because of increasing colicky pain a laparotomy was done the evening of the date of admission. A mid-abdominal transverse incision was made from the right flank to the midline and no free fluid was encountered in the peritoneal cavity. One violin-string adhesion was attached to the McBurney scar. The right tube was twisted on itself several times with gangrene of the distal two-thirds; the proximal one-third of the tube was a healthy pink color. There was no obvious cause for the twist. The tube was removed and the pathologic diagnosis was hematosalpinx the etiology of which was obscure. The patient had a smooth postoperative course and was delivered of a living female infant without complications on Dec. 4, 1950.

Vascular Accidents

1. Venous Hematomas.—

Venous pressure is increased in pregnancy, causing accidents both mild and tragic. An example of this increased pressure is the capacity of the ovarian vascular pedicle to increase over sixty times by the thirty-sixth week of pregnancy with tension of the wall of the ovarian veins increasing over two and one-half times.[18]

This pressure on the veins during pregnancy and especially during the efforts of labor may be hazardous, as pointed out by Hodgkinson and Christensen,[19] who cited 3 cases of rupture of the uteroovarian veins during pregnancy with death in 2 of the patients. Similar cases are reported to have occurred as early as ten weeks of gestation and as late as twenty-one days post partum.

An increasing number of severe intra- and extraperitoneal hematomas is being reported in the literature now; this condition may have been responsible for otherwise undiagnosed cases of sudden shock and death without postmortem proof. These more rare accidents should be kept in mind, but of present concern are the more common perigenital and perineal hematomas. Fortunate indeed is the busy obstetrician who does not have to resuture an episiotomy hematoma in the period of a year. It seems remarkable how the vascularity of a fresh episiotomy subsides immediately after birth. I think we may often suture the wound too hastily and insecurely, overlooking the fact that after sedation and anesthesia have worn off the blood pressure tends to rise and vascular activity increases. Painful stitches should not be taken too lightly and should be examined frequently. A rectovaginal examination may disclose an otherwise neglected vaginal or cervical hematoma. The episiotomy hematoma should be evacuated and resutured with interrupted sutures throughout, using a vaginal pack to act as counterpressure on the episiotomy. We prefer not to open the episiotomy wound and pack allowing healing by granulation. This healing is too long and arduous.

Case History.—Mrs. M. F., 22-year-old white gravida i, para 0, had her last menstrual period Oct. 12, 1950; the estimated date of confinement was July 23, 1951. The prenatal course was uneventful except for a five-day hospitalization in the early second trimester because of pyeloureteritis. On Aug. 1, 1951, the patient progressed normally through a seventeen-hour labor. Saddle block anesthesia was given, a left mediolateral episiotomy was done, and a living male infant was delivered by low forceps from direct occiput anterior position. In the next twenty-four hours a large episiotomy hematoma developed with considerable pain, skin tension, and ecchymosis. Under nitrous oxide and oxygen anesthesia the episiotomy was opened with removal of 100 c.c. of blood clots. The wound was resutured with interrupted chromic catgut throughout and a vaginal pack inserted. The postoperative course was uneventful and at the checkup six weeks post partum the wound was cleanly healed.

2. Cerebrovascular Accidents.—

Cerebrovascular accidents of pregnancy may be due to the chronic vascular changes of essential hypertension, the vascular lesions of syphilis, or congenital aneurysm. Eller[20] pointed out that, in the absence of chronic vascular disease, temporary vasospasm may result in distal softening of the brain with or without hemorrhage, and that certain intracranial hemorrhages are amenable to surgical approach and that early diagnosis and adequate treatment have actually been lifesaving.

Congenital aneurysms of the circle of Willis show few signs or symptoms prior to rupture and some 50 per cent of ruptures end fatally. Rhoads[21] considered such an accident as a justifiable reason for termination of pregnancy because of the increased strain on the vascular tree.

In a report of 3 cases of pregnancy complicated by subarachnoid hemorrhage, Garber and Maier[22] recognized two types of hemorrhage, primary and secondary, bleeding into the subarachnoid space from a ruptured adjacent artery constituting the former, and bleeding due to extension of intracerebral hemorrhage into the subarachnoid space the latter. A good example of the primary type is the congenital "berry" aneurysm.

The finding of grossly bloody spinal fluid is pathognomonic of subarachnoid hemorrhage. This accident during pregnancy certainly does not constitute one of the more common surgical emergencies of pregnancy, but it is added to this presentation because of the emergency of the cesarean section that was done in the following case.

Case History.—Mrs. E. F., 29-year-old white gravida ii, para i, abortions 0, had her last menstrual period Dec. 9, 1950, and the estimated date of confinement was Sept. 15, 1951. In seven prenatal examinations between April 3 and July 31 the total weight gain was 8 pounds and the blood pressure was never over 122/68. Urinalysis was normal on seven examinations except for 2 plus sugar on the next to the last office visit. The only complaint during these visits was an upper respiratory infection and slight constipation.

On August 7, at 1:30 A.M., the patient suffered a severe sudden headache and projectile vomiting and exclaimed to her husband before she lapsed into a coma, "I have a cerebral hemorrhage and am going to die." We accompanied her in an ambulance to the hospital and observed signs of decerebrate rigidity with inversion of the feet, spastic flexion of the upper extremities, and a deepening coma. The blood sugar was 160 and the carbon dioxide combining power was 48. A catheterized urine specimen showed 3 plus protein, 4 plus sugar, 1 plus acetone, and an occasional white blood cell and granular cast. A neurosurgeon was called in, and a lumbar puncture done with an initial pressure of 120 mm. water. Grossly bloody spinal fluid was withdrawn. Paraldehyde was given by rectum, with intravenous glucose, constant nasal oxygen, and suction because of considerable mucus. An emergency cesarean section set was requested but not obtained in time, so immediately after death a scalpel was found, a cesarean section was done in 30 seconds with delivery of a living male infant who recovered from atelectasis and is living and well at this date.

Summary and Conclusions

1. The incidence of operative appendicitis in pregnancy was greater in our series than is generally found in the literature.

2. An incidence of 41.6 per cent normal appendices was thought justified in order to reduce procrastination and possible rupture with its attendant increased maternal and fetal mortality.

3. Red degeneration of a myoma during pregnancy is best treated conservatively. Operative removal is rarely warranted.

4. Ovarian tumors that measure 10 cm. or more, that are bilateral, or that show evidence of progressive growth should be removed regardless of the stage of gestation.

5. An abdominal operative scar in the presence of colicky pain constitutes a situation in which intestinal obstruction is to be ruled out.

6. A painful postpartum perineum should be examined carefully for the presence of a perigenital hematoma. If found, such hematomas should be broken down, evacuated, and carefully resutured.

References

1. Meharg, J. George, and Loop, Frederick A.: Obst. & Gynec. 1: 460, 1953.
2. Meiling, Richard L.: Surg., Gynec. & Obst. 85: 512, 1947.
3. Keyes, E. Lawrence: S. Clin. North America 30: 1447, 1950.
4. Krieg, Earl G. M.: Am. J. Obst. & Gynec. 57: 736, 1949.
5. Douglas, R. Gordon: Am. J. Surg. 80: 1, 1950.
6. Greenhill, J. P.: Principles and Practice of Obstetrics, ed. 9, Philadelphia, 1948, W. B. Saunders Company, p. 450.
7. Grandin, Dean J.: Am. J. Obst. & Gynec. 57: 432, 1949.
8. Gainey, Harold L., and Keeler, James E.: Am. J. Obst. & Gynec. 58: 727, 1949.
9. Schwarz, Otto H., and Wissner, Seth: Am. J. Obst. & Gynec. 58: 1133, 1949.
10. Faulkner, Robert L.: Am. J. Obst. & Gynec. 53: 474, 1947.
11. Beck, Alfred: Obstetrical Practice, ed. 4, Baltimore, 1950, Williams and Wilkins Company.
12. Titus, Paul: The Management of Obstetrical Difficulties, ed. 3, St. Louis, 1945, The C. V. Mosby Company.
13. Greenhill, J. P.: S. Clin. North America 30: 175, 1950.
14. Philpott, Newell W.: Surg., Gynec. & Obst. 90: 557, 1950.
15. Johnston, H. W.: Canad. M. A. J. 53: 366, 1945.
16. Norton, James F., and Mangore, Edith K.: Bull. Margaret Hague Maternity Hosp. 3: 41, 1950.
17. Waters, E. G., and McCaw, William: Bull. Margaret Hague Maternity Hosp. 3: 64, 1950.
18. Hodgkinson, C. P.: Obst. & Gynec. 1: 26, 1953.
19. Hodgkinson, C. P., and Christensen, R. C.: Am. J. Obst. & Gynec. 59: 1112, 1950.
20. Eller, William C.: Am. J. Obst. & Gynec. 52: 488, 1946.
21. Rhoads, E. E.: Am. J. Obst. & Gynec. 54: 533, 1947.
22. Garber, M., and Maier, R. R.: Am. J. Obst. & Gynec. 56: 1174, 1948.

1433 Gregg Street
Columbia, South Carolina

Discussion

DR. JOHN B. VARNER, Atlanta, Georgia.—It is interesting to note that the U. S. Bureau of Vital Statistics in 1952 listed 2,600 deaths caused by appendicitis. Diseases of this organ in this day of modern hospitals, radical surgery, and antibiotics still kill 217 persons every month. Failure to recognize the condition and the injudicious use of antibiotics for an acute surgical emergency frequently lead to rupture, abscess formation, and generalized peritonitis in an abdomen poorly equipped to handle such infection.

Dr. Bryan's series and all others reported show that negligible fetal loss results from the operation of appendectomy. While it is conceivable that a Porro section might be necessary, it has not been in the series I will show you from Crawford W. Long Hospital. The figures show no maternal mortality from appendicitis, but there were several near-deaths and prolonged hospitalizations (Tables I, II, and III).

From these figures, we see that appendicitis has a corrected incidence of 1 in 727; myomectomy, an incidence of 1 in 9,000; and ovarian cyst and incidence of 1 in 3,000. The one maternal death was due to an intestinal obstruction at five months' gestation. It was decided unanimously by the Maternal Mortality Committee to be a preventable death.

Table I. Surgical Complications in Pregnancy and Puerperium, Crawford W. Long Hospital (Five-Year Period)

Total obstetrical admissions	30,519
Total deliveries	26,905
Laparotomy	100
Ureterolithotomy	2
Hematoma of vulva and vagina	34
Maternal mortality	1
(Intestinal obstruction at 5 months' gestation)	

TABLE II. LAPAROTOMY FOR SURGICAL REASONS, 100

1. Appendicitis	56	(1:480)
2. Ovarian cyst	15	(1:1,727)
3. Intestinal obstruction	9	(1:3,000)
4. Intestinal perforation	2	(1:13,450)
5. Myomectomy	3	(1:9,000)
6. Retroperitoneal hematoma	1	(1:26,905)
7. Acute salpingitis	2	(1:13,450)
8. Miscellaneous	12	
(Exploratory laparotomy 5, umbilical hernia, suspension, endometriosis, hematoma of abdominal wall, cholelithiasis, parametritis, urachal abscess, 1 each)		

TABLE III. APPENDICITIS IN PREGNANCY

First trimester	16	(29%)
Second trimester	21	(37%)
Third trimester	13	(23%)
Postpartum	6	(11%)
Total	56	Cases
Acute, pathologically proved	37	(67%)
Not pathologically proved	19	(33%)
Abortions due to operation	1	(1.8%)
Prematures (all survived)	3	(5.4%)

DR. JOHN C. BURWELL, JR., Greensboro, N. C.—The diagnostic criteria and the operative techniques employed by Dr. Bryan and his confreres are standard, but employed so infrequently as to be most profitably recalled to the attention of any audience. By way of comparison, the figure for the incidence of appendicitis during pregnancy at the Chicago Lying-in Hospital was 0.069 per cent, or essentially the same as for Columbia General Hospital.

The author's counsel regarding the management of ovarian cysts during pregnancy needs no elaboration for this group, but might profitably be taken to heart by some of the more enthusiastic of our friends doing general surgery. These gentlemen, in return, have the opportunity of furnishing advice and skill of inestimable value when the possible diagnosis of intestinal obstruction presents itself.

I am in complete agreement with Dr. Bryan regarding the prevalence and treatment of episiotomy hematomas. As a matter of fact, we had a case within the past six months which could read almost the same as his, except that I am afraid we evacuated closer to 400 c.c. than his modest 100 c.c. This patient's course was also uneventful thanks to the availability of whole blood and antibiotics.

The comparative rarity of cerebrovascular accidents during pregnancy is most fortunate for all of us. We, however, have had the misfortune of encountering two—one in a postpartum fulminating eclampsia, which resulted in immediate death; and the other in a section hysterectomy for multiple fibroids with placental separation which instigated a hemiplegia of long standing.

DR. FRANK R. SMITH, New York, N. Y.—I wish to report one patient seen in the early months of pregnancy, probably at about 3½ months in whom I found a complete torsion of the uterus. The uterus was completely twisted so that the left ovary was posterior on the left side. The patient was a primipara, not a multipara with a greatly relaxed vagina. The operation consisted simply of straightening out the torsion and performing a loose suspension so that this torsion would not recur. I saw the patient after she had been delivered and the ligaments had shortened so that it was a good suspension.

I would like to report also a case of torsion of a dermoid cyst in the ovary which also had the corpus luteum of pregnancy in it. I removed the whole ovary and carried

the patient on with corpus luteum supportive measures for five months. The patient delivered normally. About the time she delivered I had a patient with a similar cyst whom I saw before the fourth month. She refused any treatment, but went on and delivered twins.

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—Dr. Bryan's mention of dermoid cysts during pregnancy took me back to 1935 when I sat between the late Dr. Joseph Baer and the present Dr. Walter Dannreuther discussing ovarian cysts in pregnancy during my Board examination. Near the end of the interview Dr. Baer asked why dermoid cysts are particularly dangerous as a complication of pregnancy. Pedicle torsion and rupture with dissemination were mentioned—then a complete mental blank!

Another subject was introduced and discussed at considerable length. Then back to the dermoid: "Why else is a dermoid dangerous during pregnancy?" By that time sweat was dripping from my forehead and running down my back, but no additional thoughts were forthcoming. Just then the door opened, and in sauntered a very tall and, at that time, a very fat gentleman with his hands clasped across his abdomen in a characteristic manner. He asked: "Boys what are you doing to this young man?" The question was repeated to him. He replied: "Well I don't know the answer to that question myself. What do you mean?" Dr. Baer answered: "Why infection, of course." Dr. Schumann exclaimed: "Infection, why we never have infection in Philadelphia! Let's go get a coke." Of course Dr. Schumann never thought of that incident again, but since then I have been and always will be grateful to him for taking me off the hook.

A considerable portion of Dr. Schumann's life has been devoted to training young men and to getting them off the hook periodically. One result of this understanding kindness appeared at the last meeting of the American Academy. An effort to arrange a committee meeting was defeated because two committee members said, "No, we have another appointment." They were very mysterious about this and not until the next day did the truth come out. A group of former Schumann residents, including the two recalcitrant committee members, was to gather in a room to call Dr. Schumann by long distance for a marathon greeting and chat. That to me is evidence that this gentleman has had and is still having a very full life.

DR. JOHN SAVAGE, Baltimore, Md.—In regard to hematomas, I would like to suggest routine vaginal inspection immediately after routine cervical inspection following every delivery. In this way early hematomas may be discovered and treated before they reach serious proportions. There is another small but helpful clinical procedure useful in detecting early hematomas in the substance of the episiotomy repair itself. It consists of simple palpation of the area by the thumb and forefinger. Any swelling would make one suspicious of hematoma formation and appropriate steps can be taken before extensive tissue disruption occurs.

DR. BRYAN (Closing).—Dr. Varner is to be commended on his 67 per cent correct diagnosis of acute appendicitis. It shows good clinical judgment and acumen. His case histories and careful statistics bear out the fact that we all need to heed the so-called vague abdominal discomforts complained of by the pregnant patient.

Dr. Burwell questioned the time interval between the myomectomy and the delivery of twins. This interval was six weeks and we still wonder if the surgical intervention had some causative effect on the premature labor.

Vaginal hematomas, spoken of by Dr. Savage, may be clinically deceptive. In a patient with an otherwise unexplained anemia one should do a pelvic examination to avoid the possibility of missing a large vaginal or cervical hematoma, either of which might be missed by simple external examination.

DIVERTICULUM OF THE FEMALE URETHRA*

JOHN R. KIGHT, M.D., AND NORMAN N. HILL, JR., M.D., NORFOLK, VA.

(From the Department of Obstetrics and Gynecology, De Paul Hospital)

ALTHOUGH described many years ago, the subject of diverticulum of the female urethra has been neglected until recently. Kelly[1] credited William Hey with the initial description of this clinical entity in 1805, the case having been treated by him in 1786. Priestly[2] reported three cases in 1869. Though many cases have been presented since that time, neither the frequent occurrence nor the severity of symptoms has been given proper emphasis.

It has been shown repeatedly that the frequency of the diagnosis in a given locality increases many times following a presentation on the subject.[3, 4, 5] Our experience has been similar to that of others. From hospital records, the first case of diverticulum of the female urethra was treated in one of two local hospitals in 1945. Several years later a second case was admitted. After presentation of this case, 15 patients with diverticula were admitted during the following twenty-seven months. Our report is based on 10 of these cases treated in De Paul Hospital.

The history in all our cases showed that the symptoms may be severe and intermittently incapacitating. The patients had received many kinds of treatment prior to establishment of the correct diagnosis. The interval between onset of symptoms and correct diagnosis ranged from months to many years, and the therapy had consisted of medical and surgical measures. Lack of knowledge of the symptoms and difficulties with the proper diagnostic methods seem to be mainly responsible for failure in early diagnosis. Additional factors are the course of the condition, consisting of recurrent infection with spontaneous remissions, and the location of the lesion in the region of the often neglected anterior vaginal wall.

Etiology

Opinions on the etiology of diverticula in the female urethra vary.[5] It is now generally believed that true or congenital diverticula do occur, but the acquired type is much more common. It arises in the periurethral ducts and glands present throughout the length of the urethra. The existence of these glands was most satisfactorily demonstrated by Lintgen and Herbut,[6] and Huffman[7] stressed their significance in the development of diverticula.

We believe the acquired type may develop as a result of intraurethral pressure in association with one of the following processes: (1) infection of a periurethral duct or gland, (2) injury to the urethral mucosa and abscess formation such as may occur from instrumentation, electrocoagulation, or passage of a calculus, and (3) rupture of a periurethral cyst or abscess, that may or may not have had its origin in a periurethral gland by a force arising in the vagina. Pressure associated with childbearing has long been considered

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

causative. One-half of Gilbert and Cintrón's[4] patients had a history of prolonged labor or difficult delivery. Trauma produced by a retractor during a gynecological procedure would seem to deserve consideration.

Furniss[8] was of the opinion that urinary pressure due to a narrowing at the meatus was a factor in the development of diverticula and recommended meatotomy and dilatation of the meatus in all cases. As stated, we also consider the intraurethral pressure part of the process, but do not believe it need be a pressure greater than that of the normal urinary stream.

Pathology

The size of a diverticulum of the urethra may vary from a minute structure to a mass filling the anterior portion of the vagina. It may be situated just beneath or lateral to the urethra. Occasionally it is elongated and extends upward beneath the bladder. Krieger and Poutasse[9] described a "saddle" type pouch that straddled the urethra. Multilocular sacs occur. Wharton and Kearns[5] have stated that a sac may have more than one opening into the urethra and this was seen in one of our cases.

Most diverticula open into the middle or posterior third of the urethra, usually into the vaginal half of the circumference, rarely into the subpubic half. Calculi are frequently found in diverticula and were present in two of our cases.[10] Primary carcinoma of urethral diverticula has been reported by Wishard and Nourse.[11]

The distinction between infected periurethral glands and diverticula is not well defined and has been the subject of much debate. Young and McCrea[12] define the diverticulum as "a fluid filled pouch at or immediately above the vaginal introitus which is in direct communication with the urethra as shown by extrusion of pus or urine from the urinary meatus when pressure is applied to the pouch." Huffman[7] agrees that for practical purposes a lesion conforming to this description is best called a diverticulum. Skene's glands and similar glandlike structures at the meatus are not exposed to the pressure of the urinary stream as are those further up the urethra. They do not offer the clinical picture nor the diagnostic problems of the urethral diverticulum under discussion. Inflammation of these meatal ducts is often referred to as skeneitis or infected periurethral glands.

Signs and Symptoms

Pain in the region of the urethra, more marked at the time of or immediately after voiding, was the chief complaint in the majority of cases. Cook[13] emphasized the severity of urgency and dysuria in diverticula. In our experience these symptoms likewise have been proportionately much greater than in other lower urinary tract conditions. According to Gilbert and Cintrón,[4] "dyspareunia is almost always present and is the most important symptom." Leakage of urine or purulent material after voiding was frequently an associated complaint. Referred symptoms are listed by Herman and Greene[14] as "rectal irritation and pain referred to the pelvis, lumbar region, back and along the course of either ureter." Moderately severe suprapubic pain, in one patient, was relieved by surgical treatment of a diverticulum.

Diagnosis

Frequent unexplained recurrence of lower urinary tract infection should cause one to suspect a diverticulum. A mass present in the anterior wall of the vagina, in the region of the urethra, which on pressure empties urine or pus from the urethral meatus, is confirmatory. In cases in which the neck of the diverticulum is occluded or temporarily closed, a failure of extrusion may

be misleading. Since it is a collapsible pouch, absence of a fullness or mass does not rule out a diverticulum. Repeated examinations may be necessary. Two of our patients demonstrated the exact point of origin of pain when requested to do so.

A definite diagnosis of a diverticulum may be established by one of three methods. First, the opening may be visualized through the cystoscope or panendoscope. Digital pressure on the vaginal wall at the time of cystoscopy may aid in locating the entrance of the sac. Cook[13] recommends that a urethral catheter be coiled into the pocket with the injection of an opaque material to outline the cavity and its one or more openings by x-ray studies. On repeated panendoscopic examinations we were unable to visualize the mucosal opening of a suspected diverticulum in two cases.

A second method consists of performing a urethrogram. Various methods have been described in studying the urethra. A simple and satisfactory one is to insert a Foley catheter in the bladder with the tip tied off, and with a new opening cut in the catheter on the proximal side of the bulb. Slight traction is made, the urethral meatus closed by digital pressure and an opaque material injected. X-rays are taken at this time. We have been able to confirm the diagnosis in those cases in which the opening could not be demonstrated through the panendoscope by this method.

Third, a diagnosis may be confirmed by exploration alone. This we do not recommend, because of a limited knowledge of the pouch and the opening, and the rare but real possibility that one is dealing with an ectopic ureter.

Treatment

Among the many treatments recommended for diverticula are frequent evacuation by external pressure, chemical and electrocauterization, incision and drainage, and surgical removal.

In 1936, McNally[15] stated that the treatment was entirely surgical excision. He discouraged other types of obliterative procedures and this opinion is now accepted. Excision with closure of the urethral opening is believed to yield the most satisfactory results.

Our method has been as follows: Under general anesthesia, with the patient in the lithotomy position, a Foley catheter, as previously described, is inserted into the bladder. A dye is injected so as to fill the sac and urethra. A linear incision is made over the pouch and the mucosa separated from the underlying tissues. The sac is then opened, the sac wall grasped with clamps, dissected free, and excised at the neck. The urethral mucosa, urethrovaginal septum, and vaginal mucosa are then closed with interrupted sutures. Many authors recommend closure of the sac neck with a purse-string suture. In none of our cases did this method seem advisable. Even with a satisfactory urethrogram, we were still unable to demonstrate the opening into the urethra at the time of removal of the sac in 2 cases. Therefore, closure included only the urogenital layer and vaginal mucosa. Our results were successful in these 2 cases but it is our belief that the likelihood of satisfactory results is increased by mucosal closure. For this reason, we have since injected a dye just prior to excision and have allowed the catheter to remain in place for the purpose of reinjecting during the procedure if necessary to demonstrate the opening.

An indwelling catheter was left in place for several days in all but 2 cases. Two patients with small openings and small sacs voided spontaneously following the procedure.

We agree with Burns,[16] Pratt,[17] and others that suprapubic drainage is not necessary. Early ambulation and prophylactic chemotherapy or antibiotic

therapy are prescribed. Gilbert and Cintrón[4] have recently published a method of treating those diverticula that enter the urethra on the subpubic surface by a suprapubic approach similar to that utilized in the Marshall-Marchetti procedure.

Summary

Evidence has been presented that proves the necessity of more widespread teaching of the signs and symptoms and methods of diagnosing diverticula of the female urethra. Most patients have a history of much suffering and many treatments prior to obtaining a correct diagnosis.

The etiology and symptomatology of a diverticulum are the result of intraurethral hydrostatic pressure acting on a periurethral gland, cyst, or abscess that has been infected or traumatized.

A diverticulum of the urethra is a collapsible sac and may at times be temporarily occluded. Therefore, the diagnosis may be difficult even in suspected cases. In our experience, the urethrogram has been the most satisfactory method. It is recommended that x-ray studies of the urethra be done in all cases prior to surgical treatment.

Excision of the sac and closure of the urethral opening constitute the procedure of choice.

References

1. Kelly, Howard A.: Operative Gynecology, New York, 1903, D. Appleton & Co.
2. Priestly, W. O.: Brit. M. J. **7**: 1869.
3. Moore, Thomas D.: J. Urol. **68**: 611, 1952.
4. Gilbert, C. R., and Cintrón, J. R.: Am. J. Obst. & Gynec. **67**: 616, 1954.
5. Wharton, L. R., and Kearns, W.: J. Urol. **63**: 1063, 1950.
6. Lintgen, C. I., and Herbut, P. A.: J. Urol. **55**: 298, 1946.
7. Huffman, J. W.: Arch. Surg. **62**: 615, 1951.
8. Furniss, H. D.: J. Urol. **33**: 498, 1935.
9. Krieger, J. S., and Poutasse, E. F.: Am. J. Obst. & Gynec. **68**: 706, 1954.
10. Higgins, C. C., and Roen, P. R.: J. Urol. **49**: 715, 1943.
11. Wishard, W. N., and Nourse, M. H.: J. Urol. **68**: 320, 1952.
12. Young, B. R., and McCrea, L. E.: Urol. & Cutan. Rev. **41**: 91, 1937.
13. Cook, E. N.: Surg., Gynec. & Obst. **99**: 273, 1954.
14. Herman, L., and Greene, L. B.: J. Urol. **52**: 599, 1944.
15. McNally, Andrew: Illinois M. J. **69**: 234, 1936.
16. Burns, Edgar: Nebraska M. J. **35**: 246, 1950.
17. Pratt, J. Paul: Urol. & Cutan. Rev. **42**: 803, 1938.

Discussion

DR. RICHARD TE LINDE, Baltimore, Md.—I am convinced that there are many women suffering from the symptoms of a chronic bladder infection dependent upon urethral diverticulum which has not been diagnosed. Most of our cases have been examined repeatedly by urologists and the diverticulum undiscovered. The condition should always be suspected when there is persistent or recurrent cystitis.

When the diverticulum is large there is a distinct bulging into the vagina in the suburethral region. With smaller diverticula one can sometimes palpate a cushionlike area beneath the urethra. If one milks the urethra or makes pressure on the diverticulum and pus appears at the meatus, the diagnosis is made. But it is not enough simply to diagnose the diverticulum. The opening in the urethra should be visualized through the cystoscope or endoscope. This is not always easy. When the orifice is seen it can be catheterized with a small renal catheter and the diverticulum filled with dye. The picture thus obtained gives one an idea of the size and position of the diverticulum which is a great aid in excising it. We have filled some diverticula by inserting a Foley catheter into the bladder

and cutting an extra hole in the catheter just behind the balloon. The tip of the catheter is tied off so that the dye will enter the urethra instead of the bladder. Some of the dye in the distended urethra will find its way into the diverticulum and usually a good picture can be thus obtained.

In excising these diverticula it is well to open them. Thus under direct vision one can be sure of removing all of the wall and there is much less danger of serious tearing or cutting of the urethra. After closing the opening in the urethra with two layers of fine catgut the vaginal mucosa is closed with silver wire. When there has been a great deal of urethral damage considerable reconstructing must be done. In such cases I have left a polyethylene tube in the urethra and diverted the urine through an artificial fistula made into the bladder through the vagina. Such a fistula is kept open by a mushroom catheter left in place for two weeks.

Finally, I would like to say that I think this paper as well as Dr. Marchetti's yesterday demonstrates the desirability of at least some urological training on the part of the young gynecologists whom we are training today.

DR. ROBERT N. CREADICK, Durham, N. C.—Drs. Kight and Hill have chosen the most ingenious and careful of the methods employed for diagnosis and correctly insisted on accurate delineation of these diverticula prior to complete surgical excision. The authors have also done much to clarify the etiology and we can now accept the plausible answer that both congenital *and* acquired sources exist.

I have only one patient, personally followed, to report upon here: a 37-year-old white unipara attended at Walter Reed General Hospital in 1945. Her first child was born five years previously after difficult and protracted labor with midforceps extraction. Intermittent urinary symptoms dated from this time. When first seen this woman was already six months pregnant and had a large, obvious diverticulum. Dire predictions of possible urethral rupture and permanent incontinence resulted from a urological consultation and cesarean section was advised. At the onset of labor, however, we emptied the diverticulum manually, and left a soft male catheter in place, delivering the patient per vaginam without demonstrable urethral damage.

I would emphasize that leakage or actual expression of urine or purulent material from the diverticulum after voiding *is frequently followed by immediate relief of symptoms!* This helps tremendously in the differential diagnostic efforts. Might I ask Drs. Kight and Hill for further opinion regarding the obstetric aspects of this disorder?

DR. ANDREW A. MARCHETTI, Washington, D. C.—I should like to ask the essayist if he has encountered a uretheral diverticulum with two or three or more openings in the urethra, in which the urethra from the external meatus to a point beyond the diverticulosis had to be opened as an alteration to the standard technique he described.

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—This paper suggests another reason why a good gynecologist can do better work by knowing how to use a cystoscope.

In the treatment of cervical cancer, whether by radiation or by surgery, urologic studies are indicated with amazing frequency. To push off this huge volume of work which is now done in our Departmental Cystoscopic Clinic would be a tremendous imposition upon the urologists. Furthermore, the pre- and post-therapy urologic care of patients with cervical cancer adds to the interest of the problem and affords abundant opportunity for resident training.

DR. HILL (Closing).—Dr. Creadick, as far as we have been able to determine, the proper handling of these lesions complicating pregnancy is just as you outlined: that the lesion be manually evacuated and handled in that manner until delivery has been accomplished.

Dr. Marchetti, we had one case in which there were two openings from the sac into the urethra which we had been able to determine prior to the surgical excision.

Dr. Wilson, according to the literature there are approximately 10 per cent of these lesions which contain calculi and we had two cases in our own series which contained stones.

PELVIC PLASTIC REPAIR—INDICATIONS AND RESULTS*

JAMES M. WILSON, M.D., CHARLESTON, S. C.

(From the Department of Obstetrics and Gynecology, the Medical College of South Carolina)

MUCH has been written about the operative techniques of pelvic plastic surgery. Little has been said about the choice of patients, the risks involved, or whether the patient was satisfied. It is the purpose of this paper to discuss indications, risks, and results in the treatment of cystocele, rectocele, and prolapse.

Clinical Material

The period of study covers seven years, in which time 69 patients with pelvic relaxations underwent major operative repair. In going through our files for this same period, records were found on 62 individuals who had similar anatomic lesions but upon whom no operation was undertaken. Table I shows how similar were the two groups with regard to their general physical condition. Only one patient in the group not operated upon was turned down for medical reasons, the individual with heart block and five years later she was re-evaluated, considered an adequate risk, but at this time declined surgery.

Table II shows the anatomic lesions present in the two groups. There is a preponderance of cases of lesser degrees of relaxation in the group not operated upon. Yet in all of these the cervix descended at least to the spines, and in a large number there were anterior or posterior wall relaxations of some magnitude. In 9 cases in the group not operated upon there was procidentia.

TABLE I. COMPARISON OF THE TWO GROUPS WITH REGARD TO GENERAL PHYSICAL CONDITION

	OPERATED GROUP	NONOPERATED GROUP
Total	69	62
Age	54.0 (30-74)	54.6 (30-74)
Hypertension	25	13
Diabetes	2	1
Heart block	0	1
Purpura	0	1
Cerebral thrombosis	1	0

TABLE II. COMPARISON OF GROUPS WITH REGARD TO ANATOMIC LESIONS

	OPERATED GROUP		NONOPERATED GROUP	
First-degree prolapse, plus	8		32	
Cystocele		8		17
Rectocele		1		5
Second-degree prolapse plus	41		21	
Cystocele		19		10
Third-degree prolapse	20		9	

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

Indications for Plastic Repair Operations

Comparison of the presenting symptoms of the two groups is enlightening. Sixty-six of the 69 patients operated upon complained primarily of pressure. The 3 remaining also had some pressure symptoms but these were less important than the excessive bleeding in 2 cases and urinary stress incontinence in the other case.

Of the 62 patients not operated upon, 24 were seen for routine physical examinations, for cervical polyps, or for vaginal smears. Five complained largely of back pain, and 33 complained of pressure symptoms. It is of interest to note that 15 of these were fitted more or less satisfactorily with pessaries, and that 15 others with no treatment decided that their symptoms were not enough to warrant surgical repair, even though it was offered.

In other words, the main indication for the recommendation of plastic repair is the sensation of discomfort which the patient herself experiences. Menorrhagia, cervicitis, urinary stress incontinence, all are secondary to the primary indication. The only situation in which the gynecologist is justified in advising rather than offering plastic repair is in the presence of edema and ulceration of a uterus in third-degree prolapse. It is, therefore, our custom to explain to the patient, with pictures, what her difficulty is; to tell her what surgery can accomplish; and most important, to advise her what surgery cannot accomplish, such as the alleviation of back pain and nervousness.

Details and Results of Operations Performed

In considering the risk involved, it is first to be noted that standard operative procedures were used (Table III). There were no deaths in the series. Table IV shows the major operative complications encountered.

TABLE III. SURGICAL OPERATIONS PERFORMED

Vaginal hysterectomy	59
Colpocleisis	8
Colpocleisis and excision of cervical stump	1
Manchester	1

TABLE IV. COMPLICATIONS OF OPERATION

Perforation of bladder	1
Perforation of rectum	2
Operative hemorrhage, mild	3
Operative hemorrhage, severe	3
Operative hematoma in mesosalpinx	1

An interesting sidelight is the statement frequently made that previous pelvic surgery is a contraindication to vaginal hysterectomy. Table V shows the previous surgery that had been performed on those patients in whom the peritoneal cavity was explored vaginally. Five of the 8 patients on whom colpocleisis was done had had previous pelvic surgery (including one Manchester operation), but this fact had nothing to do with the choice of vaginal obliteration. There were no complications attributable to previous pelvic surgery.

TABLE V. PREVIOUS PELVIC OPERATIONS

Suspension	7
Ventrofixation of uterus	2
Supravaginal hysterectomy	1
Pelvic laparotomy, type unknown	1

Postoperative complications are shown in Table VI. Neither the hemorrhage nor the hematoma was severe, and they were easily controlled. Two of the cases of pelvic cellulitis followed surgery on patients who had had procidentia with edema and were operated upon too soon. The pelvic abscess followed a long (156 minutes) vaginal hysterectomy with unusually heavy blood loss.

TABLE VI. POSTOPERATIVE COMPLICATIONS

Postoperative hemorrhage	2
Postoperative hematoma	1
Urinary tract infection, severe	1
Urinary tract infection, moderate	3
Urinary tract infection, mild	46
Pelvic cellulitis	3
Pelvic abscess	1
Thrombophlebitis	1
Vaginal polyposis	1
Dyspareunia	2

The one severe urinary tract infection necessitated retrograde ureteral drainage, although no damage had been done to the ureters. In 75 per cent of the cases, urinary tract infection occurred, and 6 of the 69 patients were acutely ill.

Results of Operations

Table VII shows the duration of the follow-up. Fifty-nine patients were followed long enough to permit evaluation. All the technical failures listed in Table VIII were present within three months of operation, and it is felt that a year constitutes an honest minimum for judging the efficacy of the repair. While it is probable that longer follow-up would show several more symptomatic recurrences, it is believed that five or more years of freedom from symptoms justifies the risk and expense of the operation.

Table VIII represents the total failure rate as viewed by a perfectionist.

TABLE VII. DURATION OF FOLLOW-UP

Seven years	6
Six years	4
Five years	10
Four years	4
Three years	11
Two years	6
One year	18
Untraced after five months maximum	10

TABLE VIII. TECHNICAL FAILURES IN OPERATIONS

Total failure with eversion of vagina	1
Recurrent symptomatic cystocele	2
Continued pressure, anatomically normal	1
Urinary stress incontinence, unimproved	5 (Out of 22)
Posterior vaginal hernia, recurrent	2 (Out of 6)

From a practical standpoint, the results not quite so bad. The two recurrent posterior vaginal hernias were successfully repaired by subsequent operations. In only one of the failures with stress incontinence was the patient dissatisfied with the procedure as a whole, the others stating they were pleased with the result. One of the patients with recurrent cystocele said she felt better in spite of it.

Conclusion

When the indications are based on the symptoms of pelvic pressure, when the patient understands what cannot, as well as what can, be accomplished and requests operation, then, in spite of a moderate risk, the long-term end results justify vaginal plastic repair operations.

Discussion

DR. CHARLES J. COLLINS, Orlando, Fla.—The number of patients reported upon by Dr. Wilson is necessarily restricted because the decision for surgery was based primarily upon the degree of the patient's discomfort and not the degree of her prolapse or associated pathology.

It is my custom to ask my patient with relaxed pelvic supports if her discomfort and disability interfere with her normal routine of living. If they do, I have no hesitancy in advising operation. At the six months postoperative examination I ask her if she is glad she submitted to the operation. If the answer is in the affirmative, I am certain sufficient indication existed. If it is in the negative, either the indication was insufficient or the result was a functional failure. This serves as a checkrein to my overenthusiasm for operation.

Dr. Wilson states that 33 of the patients not operated upon complained of pressure and 15 of these were fitted "more or less satisfactorily with pessaries." I am sure I would have operated on more of these patients. If a patient's symptoms justify wearing a pessary for the relief of descensus she should be given the benefit of curative surgery.

Vaginal plastic surgery can be done with a high degree of safety and the patient who cannot tolerate it, regardless of age or physical state, is rare indeed. With good preoperative preparation and the use of 0.25 per cent Novocain for local anesthesia, almost any poor-risk patient can be safely managed surgically.

Dr. Wilson has done 9 colpocleises and 1 Manchester with 59 vaginal hysterectomies in his 69 operative procedures. I believe the Manchester operation is as safe as the colpocleisis particularly when done under local anesthesia, and certainly much more physiological. I am sure in a series of this kind, where disease of the uterus was not a primary consideration, my percentage of Manchesters would have been higher. I agree that previous pelvic surgery is usually not a contraindication to vaginal hysterectomy, but if I had the knowledge that my patient had a previous ventrofixation of the uterus, I would use the abdominal approach if removal of that organ were indicated. The percentage of complications may seem a little high but a discussion of this would involve pre- and postoperative management which Dr. Wilson obviously could not present in a paper of this type.

DR. CHARLES W. SMITH, Atlanta, Ga.—Many of my patients complain of suffering and discomfort that do not necessarily conform to the criterion of the author, namely, "The only situation in which the gynecologist is justified in advising rather than offering plastic repair is in the presence of edema and ulceration of a uterus in third-degree prolapse." In a large percentage of patients the chief complaints are more annoying and incapacitating than a threat to life expectancy, including stress incontinence, uterine bleeding, chronic cervicitis, sexual incompatibility, and retention of urine. I do not believe that all patients with these symptoms should be subjected to vaginal plastic procedures, but if the selected patients have previously been more or less incapacitated and otherwise confined to sedentary life, operation should be recommended.

I would like to emphasize, as has the author, that all patients who complain of pelvic symptoms regardless of their nature do not require vaginal plastic procedures unless, in the opinion of the operating gynecologist, this patient could be so rehabilitated as to become an active member of society and avoid a sedentary type of life.

DR. WALTER T. DANNREUTHER, New York, N. Y.—There are several important items connected with plastic surgical repairs to which the speaker did not refer. First, I would call your attention to an operation which is very old and which I still favor in selected cases, that is, vaginal hysterectomy done with clamps on the bad-risk patients. This operation can be done in from three to five minutes and it has been a surprise to me that even some of the older men do not seem to be familiar with this simple technique. If you wish to correct a cystocele at the same time, that can be done in another few minutes. The perineal repair necessarily has to be postponed until a later time because the clamps are in the way. I have operated on many bad-risk patients using clamps instead of sutures and so far have not had a death.

Another thing that I think should be stressed in cases of uterine prolapse is the necessity not only for three or four days of preoperative bed rest, but also packing the vagina daily with strip gauze and glycerin to produce considerable depletion from the edematous tissues.

The postoperative high incidence of urinary infections is somewhat surprising. Dr. Wilson did not say whether he used an indwelling Foley catheter or not. We usually leave one in and occasionally instill one ounce of 0.25 per cent Mercurochrome solution during the postoperative period, and our incidence of infection without the use of antibiotics has been small.

DR. NELSON B. SACKETT, New York, N. Y.—I would like to discuss two points in Dr. Wilson's interesting presentation. The first is that we at the Woman's Hospital have fallen into what I believe is an error, and I am afraid the essayist is going to justify us in that error if his remarks go unchallenged, namely, a one-year follow-up. I believe that not all the bad results will develop within twelve months. Several of our more difficult secondary plastic repairs for complete inversion of the vagina or for hernia of the cul-de-sac of Douglas, with or without enterocele, have come in the neighborhood of five to eight years after the preliminary operation, and, unfortunately, some of the primary operations were done in our own hospital.

The second point is in the list of complications which Dr. Wilson gave. I was struck by the absence of intestinal obstruction. I had one case that required laparotomy for relief of obstruction, and another that required high colonic irrigations. There was one point in reference to intestinal obstruction that the British taught us during our visits to several clinics last summer. They did not treat the peritoneum in vaginal plastic operations casually. When they sewed up the peritoneum, it was as meticulously done as in an abdominal hysterectomy.

DR. RICHARD W. TE LINDE, Baltimore, Md.—It is particularly gratifying to hear a relatively young man express a conservative attitude toward perineal plastic operations. We have spent too much time arguing among ourselves about the different techniques of curing varying degrees of prolapse, cystocele, rectocele, enterocele, etc. There are many techniques and if properly carried out by good operators all may accomplish the desired end. Perhaps we would do better to spend some of our time discussing the indications for operative interference.

I am strongly in agreement with Dr. Nelson Sackett that one year is not sufficient time for follow-up to determine the ultimate results. During the past week I have operated upon two women with recurrences following plastic operations. One of these operations was for recurrence of a prolapse 22 years after an interposition operation. The other was for an enterocele which occurred 20 years after a vaginal hysterectomy. I mention these cases to emphasize that a one-year follow-up is entirely inadequate to determine the ultimate result.

In my opinion, there are thousands of unnecessary operations done for asymptomatic vaginal relaxations. It is not clear why some women with large cystoceles have no symptoms and others with much less anatomical distortion have rather severe symptoms. I believe the decision for operation in these relaxations should be made upon the symptoms. The patient should be plainly told the nature of her condition and just what she may expect from the repair. She may then make up her mind whether she wishes the operation.

There is one exception to my rule of operating upon only symptomatic relaxations. When a vaginal hysterectomy is done it is advisable to restore the relaxed vaginal walls, even though the relaxation is asymptomatic, in order to prevent subsequent prolapse of the vagina.

DR. WILSON (Closing).—Dr. Te Linde has expressed my sentiments exactly. I would hate to see pelvic plastic surgery treated with the same recriminations as the suspension operations.

The patients in my series treated with pessaries were told what could be done for them and they preferred not to have an operation. I would have been delighted to operate on them, but they preferred a nonoperative treatment.

The incidence of urinary tract infection is quite high in our series, but I would have it understood that I was quite self-critical. Most of the 75 per cent who had urinary tract infection had a mild cystitis which responded very simply. But serious infection does occur, as it did two or three times in my experience when I was a little lax.

COMPLETE PERINEOTOMY*

C. B. CUNNINGHAM, M.D., F.A.C.S., AND J. W. PILKINGTON, M.D., F.A.C.S.,
ST. PETERSBURG, FLA.

(From St. Anthony's Hospital)

COMPLETE perineotomy may be defined as the deliberate extension through the sphincter ani or into the rectum of a median episiotomy (perineotomy) when the presenting part of the fetus jeopardizes the integrity of the external sphincter muscle or the rectal wall.

Years ago an extension of a perineal laceration into the rectum was considered to be a great catastrophe to the mother, and indeed it was considered as injurious to the physician's reputation as to the rectum. Therefore it was only natural that the lateral and mediolateral episiotomies seemed to be the answers to the problem in spite of the fact that nature always placed her episiotomy in the midline.

Although the writers were trained exclusively in mediolateral episiotomies it was felt that satisfactory approximation of the muscles was not always obtained. Many times we found very little tissue medially to which the levator could be attached.

Kaltreider and Dixon[1] in a large series reported 99 per cent satisfactory results in third-degree lacerations and D'Errico and McKeogh's[2] results were even better with complete perineotomy, although the number of cases was smaller. We followed the plan that deliberate incision of the sphincter muscle and rectum, when necessary, would allow for easier repair and better results than when the sphincter was stretched or avulsed and the rectal wall lacerated.

It is well known that the routine median episiotomy leads to extensions and lacerations of the rectum more frequently than the mediolateral episiotomy, but it has been our observation, and that of others, that these lacerations when properly repaired healed well and appeared better post partum than perineotomies of lesser degree. This we attribute to the fact that the tissues break before they are overstretched.

In our last 290 cases of primiparous patients, regardless of type of delivery, we have practiced deliberate incision of the sphincter ani externus and rectal wall when the sheath of the sphincter ani externus muscle has been stretched to its maximum length and rupture seems imminent.

D'Errico[2] listed the advantages of perineotomy as: ease of performance and repair and excellent healing; anatomical correctness; symmetrical relief of tension; production of maximum increase in available vaginal outlet with minimal incision; and lessening of trauma to the urethra by producing greatest increase in anterior-posterior diameter of the vaginal outlet; avoidance of tears of the vault in most forceps deliveries.

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

The tissues involved in perineotomy for the most part are collagenous, fibrous, and are composed chiefly of the fused layers of the superior and inferior levator fascias, urogenital trigone, and Colles' fascia. Thus the perineum is virtually a conjoined tendon.

Glasser and Waters[3] stated that the mediolateral episiotomy involves a more vascular area, therefore the blood loss is greater, formation of hematomas is more frequent, and when the incision is large it involves the fatty tissue of the ischiorectal space. In this region edema, infection, and induration are more commonly observed.

The slightly greater difficulty of repair of the mediolateral episiotomy should be no problem but even in most experienced hands the greater postpartum discomfort and subsequent dyspareunia offer distinct disadvantages. The only advantage is the protection of the rectum.

The big disadvantage of the mediolateral episiotomy involves the main argument against perineotomy—that is, extension into the rectum. When this occurs the incision has turned back toward the rectum and is extremely difficult to repair and taxes the ingenuity of the most skillful obstetrician. Eastman[4] stated that this condition occurred in 3 per cent of the mediolateral episiotomies, but he added that it is reserved for only those cases in which lacerations of the rectum are likely. The most common figure is 1 per cent by other observers.

There is more sensitivity and subsequent dyspareunia in the mediolateral scar, as multiparas who have experienced both types can testify.

Technique

The routine perineotomy is carried out and this is done with multiple mid-perineal snips. These incisions are carried to the sphincter ani externus fascia and well up the vaginal wall.

As the head is brought toward the perineum, the sphincter ani externus and the rectal wall are watched for stress. For example, when the rectum is dilated 3 to 4 cm. the head is then allowed to recede, the sphincter ani externus and the rectal wall are incised, and delivery carried out.

Repair.—The repair is carried out in a routine manner. One may use a Gelpi retractor for exposure, but it is not necessary; the rectal mucosal edges are then identified. Beginning above the apex of the rectal wound, interrupted sutures of No. 3-0 chromic catgut on an atraumatic needle are placed in the submucosal tissue about 3 mm. apart along the rectal wall down to the anus and perineum. After thorough rinsing of the gloved hands, the severed ends of the sphincter are examined. The internal sphincter, which is but a condensation of the inner circular muscle fibers of the rectum, has usually been satisfactorily reconstructed by the previous row of sutures. If additional muscle fibers are seen yet unrepaired above the external sphincter, these are united with a few interrupted sutures.

Attention is now paid to the external sphincter and this is easily identified by the deep red muscle fibers running in a fibrous canal to which it is intimately attached in its entire periphery. This sphincter capsule is united with four interrupted sutures at the inferior, posterior, superior, and anterior points. Since the levators ani insert between the external and internal sphincters, careful approximation of the capsule brings these muscles back to their normal

relationship with the rectum. The vaginal mucosa is then united with a continuous lock stitch from above downward uniting the full thickness with special care being taken to coapt the hymenal ring. The remaining perineal body is united broadly with fine interrupted sutures. The overlying Colles' fascia is united with fine interrupted sutures and the skin is approximated by application of Allis forceps, left on for about five minutes.

Postoperative Care.—The routine does not differ from that in the uncomplicated case. There is no need for prolonged liquid or low-residue diet or constipating routine. A regular house diet is enjoyed. A combination of mineral oil and milk of magnesia is given nightly after the first 24 hours. Sitz baths are given after the first 24 hours, and early ambulation is not deferred. Antibiotics are not ordered routinely, and these were not used in this series except for 4 cases (3 preoperatively with a history of ruptured membranes and a long latent period prior to the onset of labor and one because of pyelocystitis).

We believe that with proper repair and fine interrupted sutures there is a minimal chance of infection and certainly the postpartum discomfort is considerably less than with the mediolateral, especially the extensive one that continues past the anus so that the individual sits on the suture line.

Results

In the past two and one-half years we have carried out 290 deliveries in primiparous private patients at the two hospitals in St. Petersburg, Florida. Thirty-one of these cases required complete perineotomy, an incidence of 10.68 per cent. All of these patients were delivered under general anesthesia (Table I).

TABLE I. DELIVERIES IN PRIMIPARAS FROM JAN. 1, 1952, TO JULY 1, 1954

Total number of deliveries		290
No incision	9	
Perineotomy	250	
Complete perineotomy	31	or 10.68%

A review of this series of primiparas shows that age was not a contributing factor in necessitating complete perineotomy. However, contrary to the figures given in some reports[1, 5] the average birth weight was larger in those requiring complete perineotomy (Table II).

TABLE II. COMPARISON OF CLINICAL DATA IN CASES WITH SIMPLE AND WITH COMPLETE PERINEOTOMY

AVERAGE	SIMPLE PERINEOTOMY	COMPLETE PERINEOTOMY
Age (years)	23.8	25.5
Labor (hours)	7.2	15.1
Birth weight	7 pounds 4 ounces	7 pounds 14 ounces
Hospital stay (days)	5.2	5.6
Maternal morbidity	1.97%	3.2%

The figures relating to average hours of labor are misleading. Four of these patients were in labor for a considerable time before we were called and had undoubtedly been in the second stage for some time when they were first seen by us. Although the series is small we believe it is significant.

We feel that the overwhelming incidence of occiput posterior and occiput transverse positions is highly significant. Although 5 of these cases were referred to us after evidence of obstructed labor, 4 of them necessitated complete perineotomy and in 3 of these cases antibiotics had been used preoperatively. Furthermore, we believe this points to the role of the narrow forepelvis which

contributes to the necessity of complete perineotomy. The high incidence of complete perineotomy following midforceps, we feel, is also due in part to the lack of preparation of the lower birth canal. This is in accord with the findings of D'Errico and McKeogh.[2]

With regard to breech deliveries, incisions in these 2 cases were carried through the sphincter prior to delivery because of short perineums and then when the mouth and nose were over the perineal body, incisions were carried into the rectum. Short perineums were also noted in 8 vertex presentations.

The extremely low morbidity in this entire series is no doubt due to the excellent general health of these patients and conscientious prenatal care (Table III). These are reflected in both the temperature curve and the number of hospital days. In the complete perineotomy series there was one patient with pyelitis, treated with antibiotics started on the third day post partum and discharged on the seventh postpartum day.

TABLE III. METHOD OF DELIVERY AND RESULTS IN CASES WITH SIMPLE AND WITH COMPLETE PERINEOTOMY

	PERINEOTOMY			
	SIMPLE OR NONE		COMPLETE	
	NUMBER	PER CENT	NUMBER	PER CENT
Delivery				
Outlet forceps	228	88.0	20	64.5
Midforceps	12	4.6	9	24.0
Spontaneous	9	3.4	0	
Breech	10		2	6.5
Maternal mortality	0	3.8	0	
Maternal morbidity	5	1.97	1	3.2
Fetal salvage	254	98.46	31	100
Fetal mortality (entire group)		1.04%		
Maternal morbidity (entire group)		2.07%		

In the simple perineotomy series, there were 5 cases of morbidity in 259 deliveries, and these were due to upper respiratory infection, pyelitis in 2 cases, and 2 of fever of undetermined origin.

Concerning fetal mortality, there were 4 fetal deaths with none in the complete perineotomy series. The fetal deaths were as follows: (1) frank breech at term, weight 7 pounds 11 ounces, the fetal heartbeat lost two days prior to the onset of labor and delivery; (2) occiput anterior, stillborn, the fetal heart tones lost four hours prior to delivery, occult prolapse of the cord; (3) infant at term, 8 pounds, died eight hours after delivery, had bilateral polycystic kidneys; (4) premature 8 months' fetus, weight 4 pounds 8 ounces, had hyaline membrane disease, died 48 hours after delivery.

The patients with median episiotomies appeared to suffer far less perineal discomfort than other primiparas in the hospital who had been subjected to mediolateral episiotomies. There were no cases of wound sepsis, sphincter paralysis, rectovaginal abscess or fistula, or rectal incontinence.

We believe that large babies, short perineums, and narrow forepelves are indications for the necessary complete perineotomy and any one or all may be operating in any given case.

Summary and Conclusions

1. The advantages and limitations of median and mediolateral episiotomies are reviewed. The superiority of the median technique is stressed, despite the single disadvantage.

2. Two hundred ninety pelvic deliveries in private primiparous patients are analyzed, 31 of whom were subjected to complete perineotomy.

3. The perineotomy can be employed exclusively in pelvic deliveries and complete perineotomy when necessary, with excellent results and without alteration of routine postpartum care.

References

1. Kaltreider, D. F., and Dixon, D. M.: South. M. J. **41**: 814, 1948.
2. D'Errico, E., and McKeogh, R. P.: AM. J. OBST. & GYNEC. **62**: 1333, 1951.
3. Glasser, J. W. H., and Waters, E. G.: Bull. Margaret Hague Maternity Hosp. **7**: 17, 1954.
4. Eastman, N. J.: Obst. & Gynec. Surv. **3**: 828, 1948 (Editorial comment).
5. Ingraham, H. A., Gardner, M. M., and Hens, E. G.: AM. J. OBST. & GYNEC. **57**: 730, 1949.

Discussion

DR. ERIC C. SCHELIN, Richmond, Va.—During the past five years in our private practice, we have done 3,469 episiotomies, of which 1,396 were of the central variety.

While we readily admit the advent of progress in all branches of medicine, we are not aware of the colon bacillus or any of its colleagues having changed habits. As a result of this conviction, we feel that any time the rectum is unexpectedly opened, the operative field is contaminated. Consequently, our perineotomies are limited to those uncomplicated cases where we feel we can stay out of the rectum.

On occasion, we feel the perineotomy may have distinct advantages over the mediolateral variety, but we have not been impressed with any marked or enduring superiority which might offset the risks of surgery in a contaminated field. We will readily agree that almost 100 per cent of tears into the rectum will heal, when repaired by one familiar with the technique. However, it is the "almost" which disturbs us, and which we believe we have avoided with our selective use of perineotomy.

Complete perineotomy, while being sound in that it avoids contused tissues, often results in double the average number of third-degree lacerations. Careful débridement can readily be carried out with excellent results and the incidence of third-degree repairs diminished by 50 per cent or more.

In our 2,073 mediolateral episiotomies, there were no rectal tears, and in the 1,396 perineotomies, there were 6, all of which healed by primary union with good anatomical results and normal function.

While an occasional mediolateral episiotomy does not give as good a result as we had hoped for, this infrequent occurrence in no way compares with the disadvantages of a rare rectovaginal fistula, or the anxiety suffered by the doctor during the period of healing, even when that healing is perfect.

In complicated deliveries, it is necessary to explore the uterine cavity and examine the cervix. We have almost reached the point of believing that this exploration should be done routinely in all patients when proper facilities are available. We have been reluctant to do this in the presence of the surgical contamination occurring when the rectum is opened.

Our method of repair is similar to that of Drs. Cunningham and Pilkington. We feel that it is important to place the sutures of the rectal wall in the submucosa, using fine suture material on an atraumatic needle.

During the first three postpartum days, we suggest a low-residue diet; otherwise, the management is the same as for a patient without complication. We do not use antimicrobial agents routinely.

In summary, we have not had a third-degree laceration with a mediolateral episiotomy, and we believe that the postoperative results are sufficiently good, so that the added risk of only a rare rectovaginal fistula or incontinence does not warrant the routine use of perineotomy.

DR. JOHN PARKS, Washington, D. C.—The authors rightfully advocate episiotomy in preference to irregular lacerations and they adequately justify their preference for an incision through the mid-tendinous portion of the perineal body. However, to cut willfully through the external sphincter and into the rectum is carrying the procedure too far. In elective surgery one rarely intentionally opens the large bowel. Deliberate complete perineotomy is not only an operation of questionable value but an unnecessary one.

The natural extension of a median episiotomy is scarcely ever jagged. With a midline incision, irregularity of extension into the bowel is not a problem.

One of the real advantages of medan episiotomy is the fact that the incision is in the fascia and not into the muscle. Fascia supplies the fixed support of the perineal body. Muscles represent structures of mobility providing contraction, relaxation, extension, and retraction. A cut muscle necessarily retracts, leaving a depressed, fibrotic scar. Complete healing of a muscle is not immediate, but takes months. If additional room is needed at the introitus, rather than cutting through the sphincter it would seem wiser to avoid the fascial capsule by extending the incision laterally between the superficial transverse perineal muscle and the external sphincter.

In this series of 290 patients, all 31 complete perineotomies were done with the patients under the influence of general anesthesia. The need for extensive episiotomy can be avoided by relaxing the muscles of the pelvic floor. Intravenous injection of 1 to 2 mg. of a synthetic curare-like preparation, such as Syncurine, 5 minutes before delivery, will provide almost as much muscle relaxation as caudal or spinal anesthesia.

Twenty-one out of 290 patients represents a rather high incidence of midforceps delivery. Complete perineotomies were performed on patients whose labors were twice as long as those who had simple episiotomy or no incision. Midforceps delivery and longer labor bring forth the questions of how often x-ray pelvimetry was used to evaluate the pelvis, what was the average length of the second stage of labor, and what was the incidence of cesarean section during the same period of study? Certainly in midforceps delivery the patient's perineum has had no opportunity for effacement. Therefore, in the absence of some form of muscle relaxation, the incidence of lacerations or the necessity for extension of incision will be greatly increased.

In repairing incisions or lacerations involving the rectal mucosa interrupted sutures may be satisfactory, but a continuous Lembert nonpenetrating suture of No. 3-0 catgut approximating the submucosa and inverting the mucosal edges into the rectal canal seems more satisfactory. A second layer of perianal fascia is brought over to reinforce the submucosa before the levators, bulbocavernosus, superficial transverse perineal muscles, and the capsule of the rectal sphincter are reunited.

In the matter of postoperative care, sitz baths should not be necessary. Perineotomy pain results from edema and suture irritation. Edema can be prevented by the application, shortly after delivery, of an ice collar to the vulva. If the sutures are not placed immediately beneath or through the perineal skin the patient will seldom know that she had had sutures.

In 3,392 vaginal deliveries at the George Washington University Hospital in 1954, there were 38 lacerations involving the sphincter and rectal mucosa, an incidence of 1.12 per cent. The authors performed complete perineotomy almost 10 times as often as the rectum was involved by unintentional extension on our Service. Complete perineal lacerations at our University Hospital occurred in 3 instances without episiotomy; in 2 patients out of 390 with mediolateral episiotomy; and 33 times in association with 2,475 perineotomies. All complete lacerations were repaired immediately. All repairs healed primarily without infection or fistula.

The authors' report indicates that a complete incision of the perineal body properly repaired usually heals anatomically. Anatomic approximation is not necessarily followed by perfect physiologic function. In a comparative analysis, their report also indicates that they disrupted the sphincter about ten times as often as might have otherwise occurred. Complete perineotomy is certainly not a procedure which can be carried out by the in-

experienced or without the full benefit of perfect anesthesia. Even under ideal circumstances it seems an unnecessary hazard to the mother giving birth to her child. An incompetent rectal sphincter is a far more confining condition than pregnancy itself.

DR. J. J. MARSELLA, Danville, Va.—One thing might be added in connection with this paper. In Danville, under the example set by Dr. Walter McNann, we found that curare, given with the anesthetic at delivery, will often avoid the need for entering the rectum. Though we are not terrified by complete perineotomy, we feel that an enema is not adequate preparation and often, when the sphincter must be severed, if the patient has been given curare during anesthesia the severed ends of the sphincter do not retract and are easier to find.

DR. CUNNINGHAM (Closing).—Our anesthesia for the most part was given by an untrained anesthetist and for that reason we did not use muscle-relaxing drugs. The incidence of invasion of the rectum under this type of anesthesia is no greater than that of D'Errico who used spinal anesthesia.

A common definition of midforceps is necessary before we can discuss the use of forceps. Our outlet forceps are really outlet forceps with the head crowning, levator pillars separating. Whenever rotation of the head is necessary, regardless of the station, we use the term midforceps. I am sure that many of our cases listed as midforceps would, in many instances, be classified as low forceps. I do not disagree with the use of intravenous Pitocin with second-stage inertia, but it is just as easy to use forceps, rotate the head, and extract.

Although sitz baths may not be absolutely essential, they are useful where there are rectal disturbances and of value in keeping the perineum clean.

We do not believe there is immunity to the colon bacillus because that would signify something systemic. I do believe the perineum has a local tissue resistance to the bacillus, and I know of no other place in the body where a wound heals so well in a great majority of cases. With proper approximation of the tissues, the use of fine sutures, and good hemostasis, the results will be excellent.

PLASTIC RECONSTRUCTION OF THE FALLOPIAN TUBES USING POLYETHYLENE CATHETERS*

MASON C. ANDREWS, M.D., AND WILLIAM C. ANDREWS, M.D., NORFOLK, VA.

(From the Department of Obstetrics and Gynecology, the Norfolk General Hospital)

SURGICAL correction of obstructed Fallopian tubes in the infertile patient has generally fallen into poor repute because of the relatively low success rate. Greenhill[1] compiled a much-quoted success rate of only 6.6 per cent pregnancies among 818 cases of leading gynecologists.

Since this 1937 report, four developments have occurred which give a much higher expectancy of success in carefully selected cases: (1) improved techniques; (2) increased knowledge of the limitations of operations for specific types of occlusion; (3) antibiotics; and (4) the availability of an essentially nonirritating material (polyethylene) for maintaining a lumen, enclosing raw surfaces, and serving as a splint for new growth of a tube.

In spite of these adjuncts, the results, though probably much improved, are still disappointing. The proportion of patent tubes following operation is now rather high, about 70 per cent in many series, but the percentage of pregnancies is somewhat less than one-half of this figure (10 to 30).[2-8]

The failure of the patent tubes successfully to conduct and nourish an ovum may be the result of postoperative shortening and adhesions and other poorly understood factors such as interference with blood and nerve supply and peristaltic pattern.

This paper will present a brief review of recent progress in this field and add some new evidence relative to two special types of occlusion.

Previously Reported Experience

Although the different sites of obstruction are frequently combined in the same case, it seems profitable, where possible, to separate the results where a single lesion existed.

1. Obstruction Due to Peritubal Adhesions Only.—Tubal obstruction may be due only to peritubal adhesions, and patency is restored rather easily by releasing them. Rutherford[8] found this type in 7 of 42 cases operated on for obstruction, and 4 of these 7 patients became pregnant (59 per cent).

2. Obstruction at Fimbriated End.—Reported results here are generally unsatisfactory as evidenced by the figures in Table I and by the variety of procedures tried. Better results seem to follow splitting the obstructed end and everting the edges where possible in preference to amputation and cuffing.[4, 6, 8, 10]

The use of polyethylene as an obturator has apparently improved results[6, 7, 12] but formation of adhesions closed a large proportion after its removal,[6, 12] and the use of shielding materials such as fetal membranes and poly-

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

ethylene has been investigated.[5, 11, 12] Rock and Mulligan[12] have developed a polyethylene hood and demonstrated its effectiveness in improving their patency and pregnancy rates in a large number of cases. A second laparotomy is necessary for its removal.

TABLE I. RESULTS FOLLOWING SURGICAL CORRECTION OF OBSTRUCTION AT FIMBRIATED END

	TECHNIQUE	CASES	PATENT	PREGNANCIES
Ingersoll 1949	Cuff salpingostomy	18	6(33%)	0
Comninos 1954	Salpingostomy with slight eversion	21	7(33%)	6 (16%)
Rutherford 1949	Cuff or dorsal slit	16	------	11 (69%)
Gepfert 1943	Salpingostomy and allantoic membrane	28	------	3 (8%)
Ten Berge 1954	Salpingostomy and human fetal membranes	6	5(83%)	-------
Mulligan and Rock 1953	Fimbrioplasty Polyethylene hood and obturator	30*	20(67%)	5 (24%)
Castallo and Wainer 1953	Collected reports Assorted methods	23	2(8.7%)	1 (4.3%)

*Number of procedures in 21 patients.

3. Obstruction at Midportion Only.—In these cases where a normal fimbriated end is present and the total length is nearly normal, results should theoretically be excellent *if* patency could be obtained. Except in cases following tubal ligation this pure type of obstruction is relatively rare and published results are surprisingly poor (Table II). It will be noted that only 50 per cent of these in Castallo's[2] recent report had patent tubes postoperatively. In this group the polyethylene catheter should offer great improvement. Presently available reports do not confirm or refute this possibility. In 52 cases of operations to refertilize victims of Nazi sterilizations, Traenckner[24] reported only 4 successful pregnancies, 1 miscarriage, and 3 tubal pregnancies. End-to-end operations were superior to implantations. It was not stated whether a catheter was used, or following which procedures pregnancies resulted.

TABLE II. RESULTS FOLLOWING SURGICAL CORRECTION OF OBSTRUCTION AT MID-PORTION

	TECHNIQUE	CASES	PATENT	PREGNANCIES
Rutherford 1949	No catheter Early insufflation	11	-------	4 (36%)
Castallo and Wainer 1953	Assorted collected reports	26	13 (50%)	3 (12%)
Traenckner 1953	Implantation	41	15	---------
	End to-End	8	8	---------
	Total	52*	23 (64%)	5 (11%)
Milnor 1950	Anastamosis over ureteral catheter	3	-------	2†(66%)
Present report	Anastamosis over polyethylene catheter	2	2 (100%)	2†(100%)

*Only 36 cases followed up.
†Plus 1 ectopic pregnancy.

4. Obstruction at the Interstitial Portion (Uterine Cornu).—As a result of recent surgical aids, patency rates are high but pregnancy rates especially low in this lesion, even though the fimbriated end is frequently undamaged (Table III). Variations preferred by some authors include complete bivalving of the uterus for better visualization, various degrees of cornual resection, and boring the uterus with a cork bore or trephine.

TABLE III. RESULTS OF IMPLANTATION OPERATIONS FOR OBSTRUCTION AT THE INTERSTITIAL OR PROXIMAL THIRD OF TUBE

	TECHNIQUE	CASES	PATENT	PREGNANCIES
Rutherford 1949	Uterus bivalved	6	------	2 (33%)
Hartnett 1952	No catheters No insufflation for 2 to 3 months	9	7 (78%)	1 (11%)
Castallo and Wainer's collected cases 1953	Assorted	44	23 (52%)	2
Rock and Mulligan 1953	Incision cornu	63*	24 (38%)	5 (10%)
Green-Armytage 1952	Cork bore	17	------	6 (35%)
D'Ingianni 1951	Steel cannula 2 to 3 months	16	12 (70%)	5 (31%)

*Number of procedures in 48 patients.

Material, Rationale, and Results

The two types of obstruction to the relief of which this paper seeks to add evidence are: (1) obstruction at the midportion and (2) obstruction at the isthmus and interstitial portion.

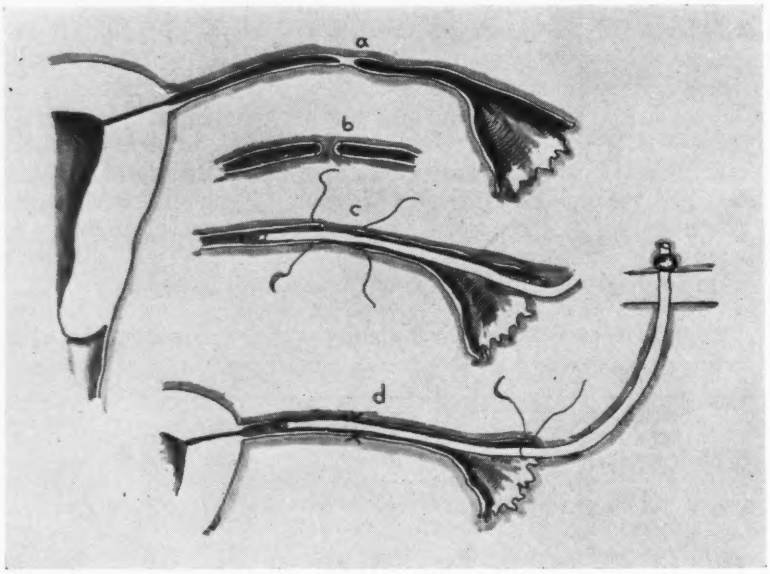


Fig. 1.—Operation for obstruction at midportion. (Method of Hellman). Occluded portion (*a*) or occluded ligated ends (*b*) excised and approximated with No. 5-0 black silk over polyethylene catheter (*c*). Catheter held in tube by No. 4-0 plain catgut stitch at fimbriated end, brought out through lower quadrant with large needle and fixed by lead shot at skin.

1. Obstruction at Midportion.—

Employing the method developed by Hellman,[7] the tubes in 2 cases of occlusion due to tubal ligation have been reanastomosed over indwelling polyethylene catheters (Fig. 1) and patent tubes and normal term pregnancy resulted in both cases. The ligated portion of both tubes was resected and the cut tub ends approximated by three No. 5-0 eye silk sutures over a polyethylene catheter which was anchored at the fimbriated end by a No. 4-0 plain catgut

suture. (A catheter of suitable size to serve as an obturator will not pass through a normal cornu. To be accessible for removal, an end must be brought through the abdominal wall or the cul-de-sac, or the cornu dilated.) The catheters were brought out through the abdominal wall and held there by a knot or lead shot. Catheters were removed in 10 and 14 days, respectively, in the 2 cases and insufflation carried out 24 hours later.

*Case 1.**—(J. H. H. No. 518303.) A 30-year-old Negro gravida vii, para vi, abortus i, who had had a Pomeroy tubal ligation in 1948 because of great multiparity, developed religious scruples and a compulsion to become pregnant. On Oct. 21, 1949, laparotomy was performed. The sealed ends of the tubes were 2 cm. apart connected only by peritoneum. These were excised and the tubes anastomosed over polyethylene catheters. The catheters were removed on Oct. 31, 1949, and a Rubin test was successful on Jan. 1, 1950. The patient conceived in August, 1950, and was delivered of a normal term baby on April 20, 1951.

Case 2.—(N. G. H. No. A72195.) A 35-year-old white, gravida v, para iv, who had undergone bilateral Pomeroy tubal ligation in 1940, remarried in 1944. She was seen in 1951 for right lower quadrant pain, diagnosed as functional associated with the desire for pregnancy. On April 30, 1951, the tubes were reanastomosed over polyethylene. On May 12, 1951, the catheters were removed and on May 15, 1951, gas passed at 40 mm. Hg. On June 21, 1951, 165 mm. was required. Subsequent Rubin tests all passed gas under 100 mm., but all showed less than normal evidence of peristaltic oscillations. A hysterosalpingogram on Nov. 21, 1951, was normal bilaterally. She conceived in March, 1952, and was delivered of a normal term baby on Nov. 18, 1952.

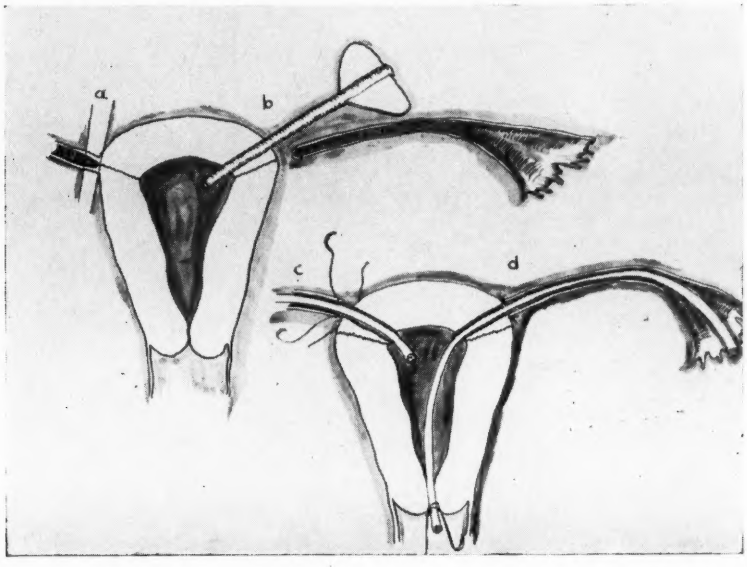


Fig. 2.—Method of correcting interstitial or isthmic obstruction without implanting distal portion. Cornu opened with cork bore and patent portion approximated to serosal surface of uterus. Indwelling polyethylene catheter sutured to cervix with silk.

She did not return as instructed for insufflation prior to attempting another pregnancy and after one year's exposure to it missed a period in January, 1955, and developed abdominal pain. Laparotomy was performed on Feb. 4, 1955, and a right tubal pregnancy found. The opposite tube looked quite healthy at the site of anastomosis but was adherent laterally to the pelvic wall and to the ovary.

*Reported through the courtesy of Dr. L. M. Hellman.

2. Obstruction at Interstitial or Isthmic Portion.—

Reference has been made to the relatively low pregnancy rate in spite of the high patency rate following implantation operations even where the distal end is normal and free. The present methods of implanting the tube may impair the physiological function in two ways: (1) shortening, and (2) interference with blood and nerve supply. These would be minimized if the patent distal portion of the tube could be attached to the *outside* of the uterus (Fig. 2) instead of sacrificing an appreciable portion in traversing the distance through the uterine wall and into the cavity with the resultant compression and torsion of mesosalpinx and tube. Could not polyethylene serve as a splint for the epithelization of an adequate new cilia-lined passage through the cornu?

Urologists have demonstrated that, if a catheter is left in a ureter in dogs and humans, the ureter will regenerate over a gap and carry on normal peristalsis subsequently.[17,18] The Fallopian tube occasionally spontaneously regenerates a functional passage after tubal ligation. Castallo[9] demonstrated that the Fallopian tube of a rhesus monkey, when severed, would regenerate over a gap of more than a centimeter if a proper splint were provided. Regeneration of tube wall occurred over steel and silver wire and polyethylene, but only with the latter was lining tubal epithelium abundant.

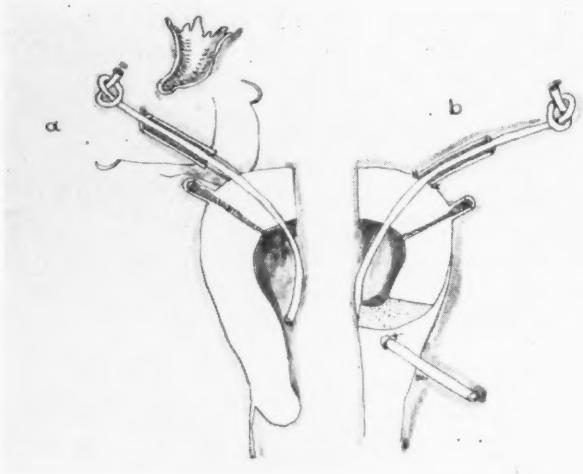


Fig. 3.—Operation performed on rhesus monkey. The tube on each side was severed near the uterus and near the fimbriated end and a polyethylene catheter threaded through it, through a tunnel made in the uterine cornu, and brought out the anterior uterine wall and fixed.

Bridging a gap free in the peritoneal cavity is not entirely analogous to following a catheter through the musculature of the uterine cornu. A somewhat similar situation is the creation of artificial lacrimal ducts by blindly passing a polyethylene catheter from the eye to the nasal space. In these cases in which the catheter has been left in place more than 30 days, patency frequently persists, indicating epithelization.[17]

Experimental formation of new interstitial tubal passage in the monkey: In the following experiment, we attempted to explore the possibility that a functional interstitial portion of tube would regenerate along a catheter without inserting the distal tube into the endometrium. At an operation, carried out on a 4,500 gram mature rhesus monkey, the tube on each side was severed near the uterus and near the fimbriated end and a polyethylene catheter threaded through it and through a tunnel made in the uterine cornu (Fig. 3). The

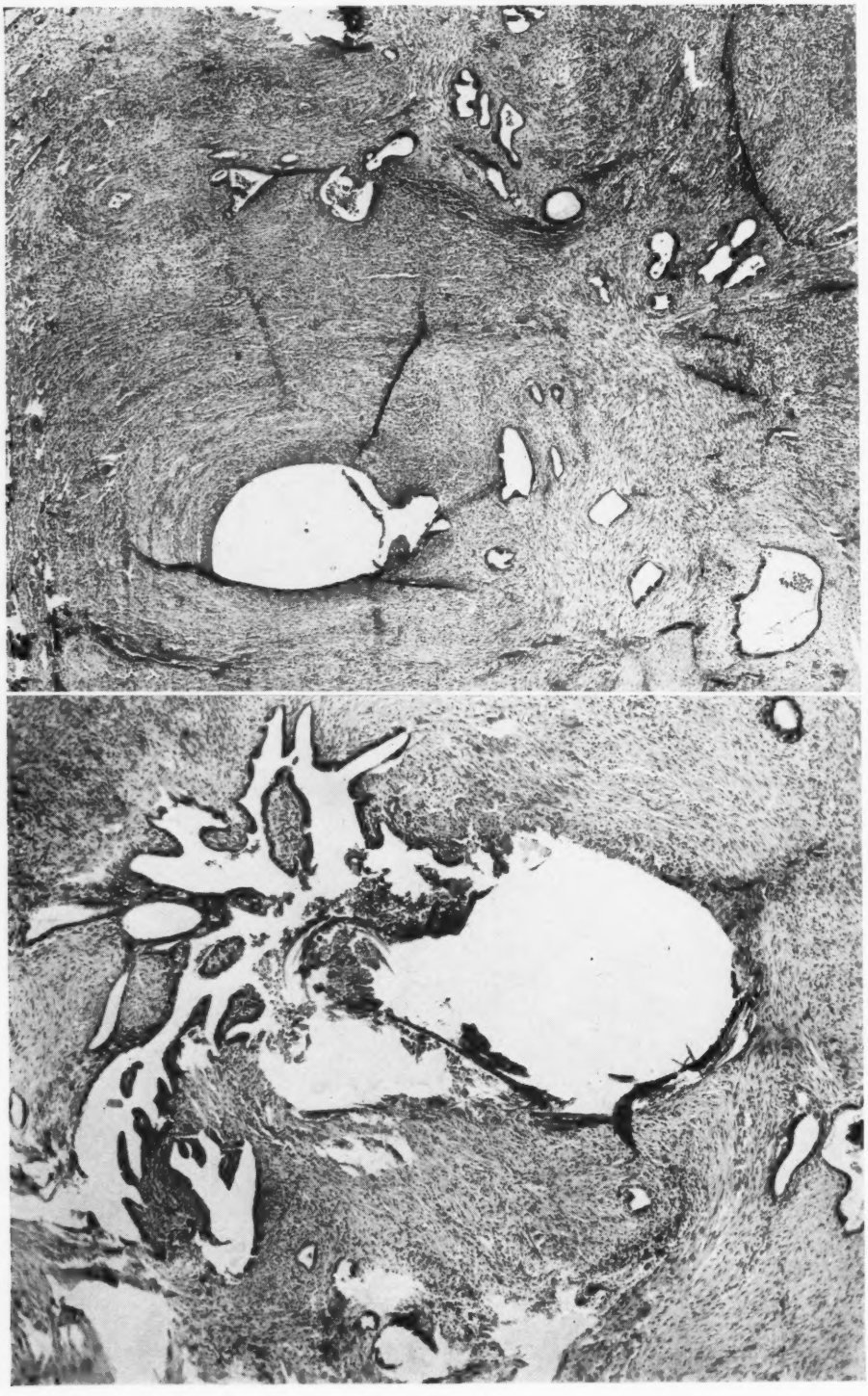
catheters were brought out through the anterior wall of the uterus and fixed by a suture to it. The tubes were sutured loosely to the serosal surface of the uterus. The catheter could not be moved in or out, and a knot marked a distance of 8 mm. from the distal severed end. Penicillin, 300,000 units, was given.

Laparotomy after 5 weeks showed that the tubes had regenerated distally 1 cm. There were dense adhesions over the anterior uterus where the catheters had been fixed with chromic catgut. Serial sections of the cornua showed tubal epithelium following the catheter to the endometrial cavity (Fig. 4). It did not completely surround the catheter in all places but seemed sufficient to assure epithelization of the cavity when the catheter would be withdrawn. The endometrium grew up into the tunnel slightly on one side but almost none on the other. Approaching the junction of the uterus and tube attachment, moving distally, a rather wild and disorderly growth of epithelium was observed, resembling salpingitis isthmica nodosa (Fig. 5, *A*). There was moderate acute inflammatory reaction throughout the tubes and especially about the sutures (Fig. 5, *B*). It is interesting that the tubal epithelium followed the path made by a suture and the suture itself (Fig. 6).

Fig. 4.—Tubal epithelium adjacent to catheter in artificial passage and partly surrounding it near endometrial cavity. The normally located interstitial tube is separated from this area by one high-powered field. (×100.)

The growth of new tube distally along the catheter, free in the abdomen, was observed by serial sections of the portion of one tube which grew over the marker knot. The order in which the tissues are encountered, moving from outside inward—and their probable order of regeneration—is as follows: First, serosa, then connective tissue (apparently with smooth muscle) appear. Much later (approximately 2 mm.) small amounts of epithelium are encountered as

A.



B.

Fig. 5.—Tubal epithelium in monkey penetrating connective tissue and muscle at site of anastomosis to uterus, resembling salpingitis isthmica nodosa. *A*, Left tube. *B*, Right tube showing marked inflammation around suture inadvertently penetrating lumen.

tubular structures in the wall, and beside it and not in the lumen. Later it is in greater quantities in the lumen, but only far back—about half the regenerated area—does epithelium surround the catheter entirely.

There is a great contrast between the orderly growth of the distal, severed end and the wild regeneration of the epithelium in many directions at the proximal end. Factors producing the latter may include the irregularly damaged opening produced by tunnelling with a clamp, the competition of various types of tissue to occupy the space, the inflammatory reaction, and the sutures.

Creation of new interstitial tubal passage in humans: In 2 patients with interstitial occlusion, a distal portion of tube was sutured to the outside of the uterus at the site of an artificially bored cornual passage, and a polyethylene catheter passed through tube and passage. In both cases a patent passage resulted and has persisted.

Fig. 6.—Tubal epithelium following path made by a stitch and growing between threads of silk suture. Catheter hole is poorly surrounded by epithelium at this superficial level. Fragments in lumen on right include remnants of epithelium damaged by removing catheter.

Case 3.—(N. G. H. No. A82166.) A 25-year-old white, gravida i, para i, who had a bilateral salpingectomy in 1945 for salpingitis sought a pregnancy of a second marriage. An Estes operation had been planned but at laparotomy on Aug. 13, 1952, a 2 cm. long stump of right tube was found present. The end was excised and the tube opened with a probe to the cornu and transected again at this point. A new passage was made at the cornu by tunnelling with a clamp, and a polyethylene catheter was threaded through the tube stump and the uterus and sutured to the cervix subsequently. The tube was fixed with No. 5-0 black silk. The edges of the distal opening were everted.

The catheter was removed on Aug. 28, 1952 (the sixteenth day), and on Sept. 2, 1952, gas passed at 180 mm. Hg. Similar Rubin tests were made on Jan. 27, 1953, March 24, 1953,

Sept. 2, 1952, April 12, 1953, and March 23, 1954, with typical graphs and shoulder pain. On Sept. 2, 1953, gas was demonstrated under the diaphragm by x-ray. On April 15, 1955 gas passed easily at 110 mm. Hg.

Case 4.—(N. G. H. No. A77488.) This 25-year-old para 0 had a dilatation and curettage on Jan. 12, 1952, because of dysmenorrhea and endometriosis. The Rubin test was negative three times. Intractable dysmenorrhea continued and on May 15, 1952, laparotomy was performed for presacral neurectomy and both tubes were found obstructed at the cornu and isthmus. The distal two-thirds of the right tube was implanted into the uterine cavity over a polyethylene catheter which was subsequently fixed to the cervix. An endometrioma was excised from the uterosacral ligament. The catheter was removed on May 26, 1952 (the twelfth day), and patency has persisted as evidenced by 10 Rubin tests. Eighteen months postoperatively she missed a period and the frog test was positive 7 weeks from the last menstrual period. She bled one week scantily after that and developed a tender mass in the left adnexa. Laparotomy on Jan. 4, 1954, because of possible ectopic pregnancy showed a dense inflammatory mass involving the left tube and ovary. The right tube (implanted tube) was quite free and normal, and patent to retrograde insufflation although closed on that day to the Rubin test. The left tube was freed and transected at the point of obstruction. A hole was made in the cornu with a cork bore and the distal tube sewed to the serosal surface of the uterus after a polyethylene catheter had been passed through the tube, uterus, and cervix. On Jan. 25, 1954 (the twenty-second day), the catheter was removed. On Feb. 6, 1954, the Rubin test was negative but gas passed easily on March 30, 1954. A hysterosalpingogram on Sept. 11, 1954, showed dye passing through the left cornu and into the tube to the mid-portion, and through the entire right tube. Subsequently gas has passed only at high pressures.

Comment

In cases where tubal obstruction is due to tubal ligation (or mid-portion occlusion) only, the success in obtaining pregnancies for indicated cases should be excellent, on the basis of the small experience reported so far, by merely approximating the ends over an indwelling polyethylene catheter with careful technique and good postoperative care. The invasive behavior of the regenerating epithelium in the experimental monkey suggests care should be taken to avoid penetrating the mucosa with the suture. The more orderly regeneration of our monkey's tube along a catheter free in the abdomen than when approximated to another healing structure supports Castallo's[2] suggestion not to approximate the cut ends but to leave them free on the catheter. Whether the physiology of the new tube wall formed over a gap is adequate cannot be told. The additional length may be of value.

In cases of cornual obstruction, the theoretical proposition that improvement in pregnancy rate may result from implanting the remaining patent portion at the serosal surface of the uterus remains to be tested clinically in a significant number of cases with normal distal portions. The evidence from the two cases here presented suggests that patency can be expected, and that from the monkey suggests the fistula will be lined by sufficient tubal ciliated epithelium. The apparent advantages would include a saving of 2 cm. in length of the tube, less displacement of it, and possibly less interference with its physiology. Several disadvantages include the tendency to the formation of epithelial pouches and slight outward penetration of endometrium at the cornu, both possibly increasing the risk of ectopic pregnancy.

If the process is carried one step farther and a gap left between the distal tube and the uterus to obtain more length, there is no present evidence that patency would result at the cornu or that the epithelium would penetrate. It is possible that the regenerated uterine cornu would surround the catheter too tightly by the time the tubal epithelium reached its depths. We would interpret the present evidence as suggesting that the preferable procedure would be boring out the cornu with a cork bore as near the interstitial tube as possible, inserting an indwelling polyethylene catheter of large diameter, suturing the muscularis delicately and accurately into the serosal opening of the uterus, and leaving the catheter in place for six weeks.

Further consideration of the behavior of tubal epithelium leads to another theoretically advantageous adjunct to tubal surgery. Two considerations are involved: (1) minimizing infection, and (2) speed of regeneration. During the proliferative phase of the menstrual cycle the epithelium increases rapidly in height, number of cells and percentage of ciliated surface. During the last 10 days of the cycle and during the menstrual period it becomes lower, less ciliated, with less cytoplasm and with extrusion of nuclei. This is a picture of regression. It seems unlikely that, during this two weeks, there is active regeneration of the epithelium at all comparable to that under estrogenic stimulation.

In spite of antibiotics there is evidence of postsurgical inflammatory reaction in tubes, even with polyethylene. Minimizing this should make healing more physiological. In a study of postpartum tubes we[20] have demonstrated previously that 67 per cent develop an inflammatory reaction normally, with 39 per cent showing microscopic salpingitis (Table IV). However, no such reaction was found in any of 12 patients who had received stilbestrol during the puerperium.

TABLE IV. INCIDENCE OF SALPINGITIS IN 36 CASES OF PUERPERAL STERILIZATION BETWEEN THE FIFTH AND FIFTEENTH POSTPARTUM DAYS

	NUMBER CASES	SALPINGITIS	MINIMAL INFLAMMATORY REACTION	TOTAL INFLAMMATORY REACTION
Unmedicated	24	9 (39%)	7 (28%)	16 (67%)
Stilbestrol treated	12	0	0	0

For both these reasons it seems that it would be preferable to maintain the epithelium in the proliferative, estrogen-stimulated stage after operation. It was our practice in 3 of the cases described to give stilbestrol to block ovulation and to continue medication while the catheter is in place.

Information from another source suggests that certain physiological variations greatly favor spontaneous regeneration of a functional Fallopian tube. Following puerperal sterilization, pregnancy was found by Prystowsky and Eastman[21] to be remarkably common when the procedure was performed with cesarean section or hysterotomy (1 in 59) whereas the failure rate was only 1 in 607 when sterilization was performed more than 18 hours post partum (Table V). It seems likely that some factor or factors peculiar to pregnancy exert an influence favoring regeneration. This could be the quantitative increase

of cortisone, progesterone, or estrogen or a combination thereof. Hellman[22] suggested that a delay produced by cortisone in the closing of the tubes by healing might be responsible.

Our present practice is to use cortisone in small doses postoperatively for tubal plastic procedures in spite of its slightly adverse effect on healing of the abdominal wound. The inhibitiory action of cortisone on connective-tissue growth is well known and yet the epithelial regeneration is not so inhibited. It appears that both circumstances would facilitate patency of the healing tubes. Our observations[26] indicate that estrogen-stimulated proliferation of tubal epithelium still occurs in patients given therapeutic doses of cortisone although not in patients receiving progesterone.[20]

TABLE V. PREGNANCY FOLLOWING POMEROY TUBAL LIGATION ACCORDING TO INTERVAL FROM DELIVERY TO STERILIZATION*

TIME	CASES	PREGNANCIES	RATE
0-1 hour (Cesarean or hysterotomy)	400	7	1:57
1-18 hours	413	2	1:207
Beyond 18 hours			
Puerperium	607	1†	1:607
Interval	56	0	-----

*Figures from Prystowsky and Eastman.[21]

†The patient received progesterone 100 mg., intramuscularly every day from delivery to operation on postpartum day 5 (the only patient in entire series so treated).

Summary

1. Two cases in which Fallopian tubes, obstructed by tubal ligation, have been reanastomosed using polyethylene catheters are presented. Patent tubes and normal term pregnancies resulted in each case.

2. For correction of interstitial obstruction, a theoretically advantageous method of anastomosis to the serosal rather than endometrial surface of the uterus is described.

3. Evidence is presented to suggest that patency and lining through the cornu with ciliated epithelium may be expected following this procedure.

4. Observations on the regeneration of the Fallopian tube of the rhesus monkey along a polyethylene catheter are presented.

5. Evidence is presented which is interpreted to indicate that maintaining the tubal epithelium in the thick, proliferative, heavily ciliated state postoperatively may enhance regeneration and inhibit infection.

We wish to express appreciation to Dr. L. M. Hellman for stimulating and aiding our interest in this subject and for permission to use Case 1 with which operation one author assisted him. The important help of Drs. Arnold Strauss, Robert Faulconer, and George Verecska of the DePaul Hospital Pathology Department, and of Dr. F. E. Perkins is gratefully acknowledged.

References

1. Greenhill, J. P.: AM. J. OBST. & GYNEC. 33: 39, 1937.
2. Castallo, M. A., and Wainer, A. S.: AM. J. OBST. & GYNEC. 66: 385, 1953.
3. Comninos, A. C.: Fertil. & Steril. 5: 334, 1954.

4. Ahumada, J. C., Raul, M. C., and Mezzadra, J. E.: Semana med. 58: 248, 1951, Quoted in Greenhill, J. P., editor: The 1951 Year Book of Obstetrics and Gynecology, Chicago, 1951, The Year Book Publishers, Inc.
5. Ten Berge, B. T.: Fertil. & Steril. 5: 339, 1954.
6. Mulligan, W. J., Rock, J., and Easterday, C. L.: Fertil. & Steril. 4: 428, 1953.
7. Hellman, L. M.: Fertil. & Steril. 2: 498, 1951.
8. Rutherford, R. N., Lamborn, H. M., and Banks, A. L.: Am. J. Obst. & Gynec. 58: 673, 1949.
9. Castallo, M. A.: Fertil. & Steril. 1: 435, 1950.
10. Ingersoll, F. M.: New England J. Med. 241: 686, 1949.
11. Gepfert, J. R.: Am. J. Obst. & Gynec. 44: 1031, 1943.
12. Rock, J., Mulligan, W. J., and Easterday, C. L.: Obst. & Gynec. 3: 21, 1954.
13. Hartnett, L. J., and Hartnett, D. C.: Am. J. Obst. & Gynec. 64: 637, 1952.
14. Green-Armytage, V. B.: Brit. M. J. 1: 1222, 1952.
15. D'Ingianni, V., and Fontenelle, I. L.: South. M. J. 44: 1139, 1951.
16. Doyle, J. B.: Fertil. & Steril. 2: 475, 1951.
17. Davis, A. M., Strong, G. H., and Drake, W. M., Jr.: J. Urol. 59: 851, 1948.
18. McIver, R. B.: J. Urol. 43: 1069, 1939.
19. Henderson, J. W.: A. M. A. Arch. Ophth. 49: 182, 1953.
20. Andrews, M. C.: Am. J. Obst. & Gynec. 62: 28, 1951.
21. Prystowsky, H., and Eastman, N. J.: J. A. M. A. 158: 463, 1955.
22. Hellman, L. M.: Personal communication.
23. Weisman, A. I.: Am. J. Surg. 82: 278, 1951.
24. Traenckner, K.: Arch. Gynäk. 4: 387, 1953.
25. Milnor, G. C., Bowles, H. E., and McCorriston, C. C.: Proc. Staff Meet., Clin. Honolulu 16: 29, 1950.
26. Andrews, M. C., and Andrews, W. C.: Unpublished data.

Discussion

DR. DEBORAH C. LEARY, Chapel Hill, N. C.—I am forced to discuss this paper from a purely theoretical standpoint since, to date, at Chapel Hill, we have not found any suitable candidates for plastic procedures on the tubes other than the incidental freeing of peritubal adhesions during laparotomy done for other causes and hence we have had no experience with the use of polyethylene catheters. Nevertheless, the incidence of tubal ligation for multiparity, freely interpreted in North Carolina as three full-term pregnancies, is so high that we may expect to see patients of the relatively favorable type described by Dr. Andrews in his first two cases, and I concur in his suggestion that a supply of sterilized polyethylene catheters and hoods, as described by Rock, would be a useful adjunct to the gynecological armamentarium.

In the management of noniatrogenic tubal blockade, reported results have certainly been discouraging even with the use of polyethylene. There is no question in many of these cases but that the entire physiology of the tube has been so distorted by disease that the simple establishment of patency is not adequate to produce satisfactory results. In this connection, I believe that Dr. Andrews' suggestion that shortening be minimized in correcting corneal obstruction by a serosa-to-serosa anastomosis over polyethylene is an important one, since it seems quite possible, from what we know of the physiology of the fertilized ovum, that too short a tube may dump it into the uterine cavity before it is ready to implant.

Dr. Andrews' demonstration of the willingness of tubal epithelium to follow any sinus tract, even that set up by a suture, re-emphasizes the importance of careful handling of these tissues and the avoidance of penetration of the muscularis by suture material.

His suggestion, based on the work of Novak and Everett and his own previously reported studies on puerperal tubes, that the tubal epithelium be maintained in an estrogenic, proliferative state in which its growth is most rapid and its resistance to infection highest, seems to me a very valuable adjuvant which should certainly be employed whenever this type of surgery is contemplated.

DR. HENRY C. FRECH, Savannah, Ga.—We have all encountered women who have had previous tubal ligations that they wish had never been done, and they are seeking to have this condition corrected. In the past we have had to tell them that nothing could be done. Now with the use of polyethylene tubing, antibiotics, and stilbestrol, it may be possible to re-establish the patient's ability to reproduce.

Dr. Andrews' suggestions regarding the correction of obstructions at the cornu and fimbria are worthy of trial. More attempts should be made to relieve these tubal obstructions surgically than has been done in the past. However, we should have the patient and her husband sign a statement that they request the operation with full knowledge that they may expect a living child in only 5 to 10 per cent of the cases.

DR. ROBERT S. HOWELL, Miami, Fla.—Since the advent of polyethylene I have done six tuboplasties using polyethylene tubing to canalize both the uterus and the tubes. All of these patients had suffered tubal obstructions, secondary to varying degrees of salpingitis and/or pelvic inflammatory disease. There has been a successful delivery of a normal infant in one case, thirteen months ago, and this patient is now pregnant again, some ten to twelve weeks. Two others aborted.

I cannot believe that shortening of the tubes plays very much of a role in the final end results in these cases. This belief is based upon 2 cases of ectopic pregnancy which occurred on my service in the last three years. The tubal ruptures occurred in the proximal interstitial portion of the tubes in women on whom Pomeroy types of sterilizations had been carried out five and eight years, respectively, prior to their accidents.

The inertness, and the almost complete lack of tissue reaction in animal as well as human tissue resulting from the use of polyethylene tubing has been proved by a number of different investigators and there remain much misinformation and misunderstanding regarding the physiology of the Fallopian tubes, the method of entry, and the travel influence of the ovum.

HIATUS HERNIA IN PREGNANCY*

COURTNEY D. EGERTON, M.D., AND ROBERT J. RUARK, M.D., RALEIGH, N. C.

(From the Rex Hospital)

HIATUS hernia is not a common complication of pregnancy, but the condition is not nearly so rare as its diagnosis. Rigler and Eneboe[1] made x-ray studies on 195 women in the third trimester of pregnancy. These women were chosen at random, with or without gastric symptoms. Of 116 multiparas examined, hiatus hernia was demonstrated in 21 (18.1 per cent); in 79 primiparas, 4 were found (5.1 per cent). The combined incidence was 12.8 per cent. Of 10 positive cases re-examined after delivery, the hernia could be demonstrated in only 3.

In all probability, diaphragmatic herniation of part of the stomach in the pregnant woman is responsible for more epigastric distress and pain than is realized.[2] Conversely, perhaps the great majority of such hernias cause no symptoms at all. In Rigler and Eneboe's study no correlation between gastric symptoms and the presence of a hiatus hernia could be determined.

The symptoms are varied. They may take the form of persistent nausea and vomiting which does not abate after the third month. Occasional patients will have hematemesis. In many, the chief complaint will be intractable "heartburn" developing after the twentieth week, progressing until delivery.[3] A usual feature is the aggravation of symptoms when recumbent.

When such symptoms are severe they present a very trying problem for both patient and doctor. We have had the misfortune of encountering two such cases of symptomatic hiatus hernia in pregnancy within the same year.

CASE 1.—Mrs. H. L. (No. 49846) was a 35-year-old white para i, gravida ii, whose last menstrual period was Nov. 1, 1952, and the estimated date of confinement Aug. 8, 1953. Her first pregnancy eight years previously had been uncomplicated. Her past history was essentially negative except for chronic indigestion and vague epigastric pains. She had had a complete gastrointestinal series in another town in 1950 and this was reported as "negative."

The patient lived in a town about 50 miles from Raleigh and received prenatal care from her family physician through the first six months of her pregnancy. She was then referred to one of us (R. J. R.) for further management and delivery. She had had persistent nausea, vomiting, "heartburn," and anorexia throughout her pregnancy. Although she denied hematemesis, the hemoglobin on May 12, 1953, was only 10.5 Gm. (68 per cent). Her weight gain had been only slight, and the blood pressure and urinalysis were normal. In the next 10 weeks the gastric symptoms became progressively worse in spite of conservative medical treatment. During that time she lost about 5 pounds in weight, and became more anemic and fatigued. By July 21, 1953, she was unable to retain anything by mouth and was admitted to Rex Hospital for studies and supportive therapy. On admission the hemoglobin was only 8 Gm. (52 per cent). She was transfused with 1,500 c.c. of blood in the next three days. An upper gastrointestinal series on July 22 showed a hiatus hernia measuring 4 cm. in diameter.

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

On July 26, the hemoglobin was up to 12 Gm. (78 per cent) and, conditions being "ripe" for induction of labor, the membranes were ruptured artificially. After an easy five-hour labor under continuous caudal analgesia, a living 5 pounds 8 ounce female infant was delivered spontaneously. The patient had a normal puerperium and was discharged on Aug. 1, 1953, the sixth postpartum day.

Follow-up on this patient one year later discloses that she still has much dyspepsia and anorexia with frequent vomiting. She can tolerate only bland foods and only in small quantities. A follow-up barium swallow on Nov. 17, 1954, showed the hernia still present. Operation has been considered but further medical management is being tried at present.

CASE 2.—Mrs. R. McG. (No. 57799) was a 29-year-old white gravida iv, para ii, abortus i, whose last menstrual period was May 5, 1953, and the estimated date of confinement Feb. 12, 1954. Her past history showed that she had had persistent nausea and vomiting throughout both of her previous full-term pregnancies and in the second one she had even vomited blood which had been attributed to esophageal varices. X-rays taken at another hospital four days after her second delivery were reported "negative." She had had no gastric complaints between pregnancies.

She registered for prenatal care in August, 1953, and at that time was found to be in the fourth month of gestation and in good condition except for persistent nausea and vomiting, usually worse when lying on her back. The serologic test was negative, blood count normal, Rh factor negative. The vomiting failed to respond to the usual antiemetic treatment and in late November she began to vomit small amounts of bright red blood. She was referred to an internist in consultation and an upper gastrointestinal x-ray on December 5 showed "a small but definite hiatus hernia." No treatment other than a bland diet and frequent small feedings was instituted. She continued to vomit an estimated 2 ounces of blood about twice a week for the remainder of her pregnancy. Periodic blood counts remained at about 80 per cent hemoglobin. Anti-Rh titers remained negative.

On Feb. 5, 1954, labor was induced by rupture of the membranes and Pitocin infusion under continuous caudal analgesia. A living 7 pounds male infant was delivered by outlet forceps after six hours of labor. A barium swallow on the fourth postpartum day still showed the hernia although the patient's gastric symptoms had disappeared completely. She has been completely asymptomatic ever since delivery and in November, 1954, nine months later, a repeat barium swallow failed to demonstrate the hernia.

Comment

A congenital weakness at the hiatus is probably a prerequisite just as in hernias elsewhere. Increased intra-abdominal pressure is certainly contributory, especially if repeated as in multiple pregnancies. As mentioned before, posture plays a large part in the symptoms of these hernias and that is especially true in the gravid patient. For that reason, if a hiatus hernia is suspected, x-rays should be taken with the patient in the supine position. When upright, these hernias tend to reduce themselves.

The two cases just presented represent a good cross section of the clinical picture presented by a hiatus hernia in pregnancy. In one, the chief symptoms were dyspepsia and anorexia with resultant nutritional anemia. In the other, hematemesis was the chief complaint. In one the hernia is still present and giving symptoms; in the other a spontaneous "cure" was obtained after delivery.

We have recently encountered a third case completely unlike these two. This patient had no symptoms at all until one hour post partum when she complained of dull, constant pain just behind the xiphoid process. Barium swallow revealed a hiatus hernia. It is possible this hernia developed only under

the increased pressure of the patient's expulsive efforts in the second stage of labor. Frankly, the diagnosis was considered only because this paper was in the process of being written. This case is mentioned merely to emphasize the fact that hiatus hernia should be considered whenever bizarre or persistent gastric complaints are encountered in pregnancy.

References

1. Rigler, L. G., and Eneboe, J. B.: J. Thoracic Surg. **4**: 262, 1935.
2. Schnepp, K. H.: AM. J. OBST. & GYNEC. **46**: 142, 1943.
3. Evans, J. R., and Bouslog, J. S.: Radiology **34**: 530, 1940.
4. Mengert, W. F., and Murphy, D. P.: Surg., Gynec. & Obst. **58**: 150, 1934.

714 SAINT MARY'S STREET

BILATERAL ECTOPIC FUSED KIDNEY IN PREGNANCY*

ERNEST W. FRANKLIN, JR., M.D., CHARLOTTE, N. C.

(From Charlotte Memorial Hospital)

BILATERAL ectopic fused kidney in pregnancy is a relatively rare occurrence. Anderson[1] in his review of the literature to 1948 reported only 5 cases, and none have been reported subsequently. Anderson states that the outlook for the mother with this condition has improved, but the fetal mortality has been about 15 per cent. The incidence of abortion and prematurity was the same as that found in uncomplicated pregnancy.

Case Report

A white 29-year-old primigravida, married six and one-half years, was found to have a fused ectopic kidney as shown by x-ray (Fig. 1).

She had had an appendectomy in 1945, but at that time no mass in the abdomen was noted. In 1948, she had an exploratory laparotomy for an undiagnosed mass in the abdomen, identified as an ectopic kidney. Urinary tract infections occurred in February, 1952, and May, 1953.

The last menstrual period occurred on Nov. 13, 1953. On Jan. 26, 1954, she threatened to abort, but was successfully treated with Lutocylol, 10 mg. linquets twice a day, and six days of bed rest.

At the time the patient was first seen, she was having no urinary symptoms, but she did have a bacilluria. Urine culture studies made on Jan. 8, 1954, showed (1) beta streptococci, (2) hemolytic and nonhemolytic *Staphylococcus aureus,* (3) hemolytic *B. coli.* The Mosenthal concentration test was normal, the blood nonprotein nitrogen 28 mg. per cent, and the blood sugar 79 mg. per cent. She was treated at this time with antibiotics and the condition of the urine improved.

Physical Examination.—A mass seemed to be palpable in the midline, ill-defined and not particularly mobile, a point of differential importance between ptosed and ectopic kidney since the former is characteristically mobile.

On bimanual pelvic examination, a mass was found lying in front of the junction of the last lumbar vertebra with the sacrum. The distance between the lower margin of this mass and the top of the symphysis pubis was approximately 6 cm. It was thought that this would allow enough space for the pregnant uterus to rise between the mass and the symphysis and become an abdominal organ as the pregnancy progressed. The uterus itself was very indistinct and soft.

The patient's course was uneventful except for the threatened abortion previously mentioned. It is stated that patients with ectopic kidneys frequently have considerable backache and some referred pain down the back of the legs, but this patient complained but little of either and had no dysuria.

X-ray examinations at term (Fig. 2) indicated that the kidney had been displaced upward and out of the pelvis. We waited ten days after the expected date of confinement and decided that abdominal delivery was the procedure of choice.

On Sept. 1, 1954, a classical cesarean section was performed at Charlotte Memorial Hospital. The preoperative diagnosis was breech presentation; fused ectopic kidney.

Procedure.—Under spinal anesthesia, the abdomen was prepared, opened, and the old scar removed in the usual manner. A full-term gravid uterus of the arcuate type was

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

disclosed. The classical midline incision was made in the uterus and the baby was delivered and cried instantly. The placenta was removed intact and the uterus closed with two layers of continuous sutures.

A large retroperitoneal mass, somewhat kidney-shaped, was found just above the promontory, lying across the lower lumbospinal column. It was approximately 6 inches from side to side and 4 in width. A large broad-mouthed Meckel's diverticulum was found but not removed. The patient withstood the operation well and was returned to her room in good condition.

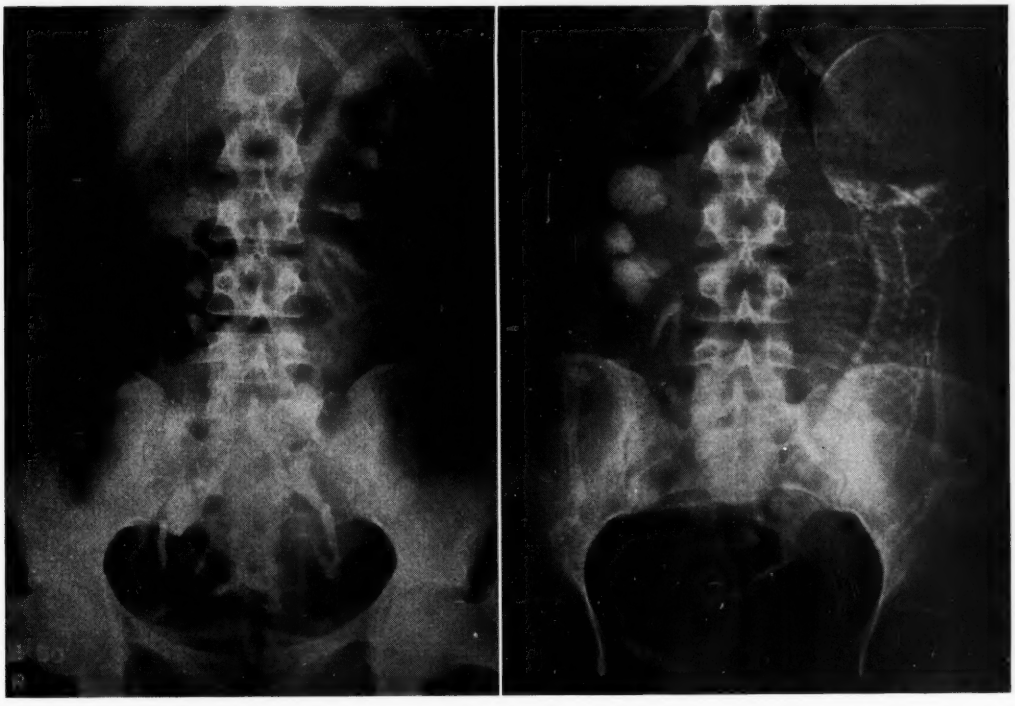


Fig. 1. Fig. 2.

Fig. 1.—A prenatal retrograde pyelogram visualizes the location of the fused kidneys in the pelvis with short ureters.

Fig. 2.—Pyelogram near term showing kidney with dilated calices displaced into right flank; fetus presenting by the breech.

Post Partum.—The immediate postpartum course was normal. The patient nursed her baby. The laboratory examination of urine and phenolsulfonphthalein renal function tests were normal.

At six weeks post partum, the patient was still nursing her baby and had no pelvic or urinary complaints. Upon abdominal examination, a mass was encountered just below the umbilicus extending about 8 cm. bilaterally from the mid-line and about 10 cm. from top to bottom. It was not tender. Pelvic examination showed normal external genitals and vagina; the uterus was anterior and in the midline, freely movable, with no marked tenderness.

Summary

1. A 29-year-old primigravida, with fused ectopic kidneys of pancake type was allowed to proceed with pregnancy.

2. The uterus became an abdominal organ in spite of a fairly immovable ectopic kidney mass with extremely short ureters. At the same time the kidney mass also moved from the pelvis to the abdomen.

3. The patient was delivered by classical cesarean section ten days past her expected date of confinement of a 6 pound 12 ounce normal male infant with an unfavorable breech presentation.

4. The postpartum course was uneventful and the kidney mass returned nearly to its prenatal position.

Reference

1. Anderson, G. W., Rich, G. G., and Harris, B. A., Jr.: J. Urol. **65**: 760, 1950.

INTRAUTERINE RUPTURE OF FETAL VESSELS DURING LABOR*

JOHN P. MICHAELS, M.D., M.Sc., F.A.C.S., ORLANDO, FLA.

(From the Departments of Obstetrics and Pathology, Orange Memorial Hospital)

A REVIEW of the literature discloses only a small number of reported cases of rupture of fetal vessels at the onset of or during labor. It is the purpose of this report to call to the attention of obstetricians that this accident is not a rarity and is indeed far more common than suspected. Torrey[1] in 1951 remarked that there were probably not more than 100 cases cited in the literature. In 1954 Beer[2] was unable to find a subsequent reported case in the American or British literature. Three such cases are herein reported.

It is indeed noteworthy that three members of the South Atlantic Association of Obstetricians and Gynecologists have added to the sparse data on this complication, namely, Dr. M. P. Rucker,[3] Dr. E. W. Groseclose,[4] and Dr. John Fish.[5]

The large majority of contributors to the literature are chiefly concerned with the entity known as vasa previa. This abnormality may be best explained by the concept of extension to the fetus of an umbilical cord in which the vessels course through the membranes unsupported and exposed by the placenta and usually overlie the internal os.[3] This condition is invariably associated with a velamentous insertion of the cord. The cord supposedly arises very early in pregnancy from the most vascular portion of the chorion. Should this occur in the region of the decidua capsularis, and the placental development be subsequently shifted to the decidua basalis, the vascularity of the decidua capsularis decreases and that of the basalis increases, resulting in velamentous insertion.

The incidence of velamentous insertion of the cord has been variously reported as being between 0.24 and 1.25 per cent. I have long been interested in the placenta and cord and have recently surveyed some 1,000 consecutive and unselected deliveries at the Orange Memorial Hospital at Orlando, Florida. Our incidence of velamentous insertion of the cord in this institution was 14, or 1.4 per cent. Under this heading one must also include vessels running to a succenturiate lobe or between the lobes of a multipartite placenta. The incidence naturally increases in proportion with multiple pregnancies. As Wickster[6] has pointed out, whether or not a woman is in labor or has a vertex or breech presenting is not essential to this definition. It must also be understood that the overlying vessels may rupture before, at the onset of, or during labor, not necessarily resulting in rupture of the membranes. Kosmak[7] cited a case wherein a velamentous insertion of the cord ruptured near the entry of the vessels into the upper pole of the placenta in the fundus of the uterus. Groseclose[4] reported a case of vasa previa in a twin pregnancy with rupture

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

of vessels of the first fetus resulting in death from exsanguination. Leff[8] reported a hemorrhage from a ruptured varicosity which resulted in the death of the fetus. Rupture of the umbilical vessels which do not cross the internal os may result from excessive traction on a short umbilical cord. Busby and Neal[9] cited a case of near-exsanguination of the fetus due to an umbilical tear of a small vein at the marginal insertion of the cord as a result of overstretching of a short cord around the neck at the time of delivery.

The diagnosis of intrauterine rupture of fetal vessels is a most difficult one to make. As Torrey[1] has pointed out, one must first have a "high incidence of suspicion." This would be most difficult to maintain over the usual high incidence of placenta previa, rupture of a marginal sinus,[9] and abruptio placentae. The onset of painless vaginal bleeding, however slight, accompanied by irregularities in the fetal heart tones is strongly suggestive. A smear of this bloody fluid may reveal normoblasts or nucleated red blood cells which would definitely add to the diagnosis.

Fig. 1.—Photograph of gross specimen. Note the arrow pointing to a ruptured aneurysm of a fetal vessel which resulted in a fatal intrauterine exsanguination.

While rupture of the fetal vessel entails no particular danger to the mother, the outcome to the fetus is exceedingly grave. The fetal mortality is probably far in excess of 50 per cent. Given a pallid infant at birth, one should always consider the possibility of exsanguination due to a rapid blood loss from a rupture or tear of a fetal vessel. Many a case of so-called asphyxia pallida has undoubtedly been misdiagnosed as due to cerebral damage or severe anemia of erythroblastosis. In our teaching program at the Orange Memorial Hospital we attempt to emphasize the value of a minute and prompt examination of every cord and placenta for tears or ruptures at the time of delivery.

Once the diagnosis is suspected or made, prompt treatment is of the utmost importance. Shock and hypoxia of the infant should immediately be combated by heat and oxygen. It is the responsibility of the obstetrician and/or pediatrician to institute a prompt blood transfusion. Ten cubic centimeters of blood per pound of body weight should be drawn at once from the mother, and, should she be Rh positive, given to the infant preferably through the umbilical vein by means of a No. 17 polyethylene catheter. If the mother is Rh negative, a plasma infusion should be instituted until Rh-negative blood is obtained. When time permits, the infant's blood status should be determined and the necessary amount of proper type and Rh factor blood given.

A brief résumé of representative cases is herewith submitted.

Fig. 2.—The fetal surface of the placenta showing a velamentous insertion of the cord with rupture of the umbilical vein. The wall of this vein microscopically was thin and imperfectly developed.

Spontaneous Intrauterine Rupture of Varicosity of a Small Fetal Vessel, With Fatal Exsanguination.—

CASE 1.—Mrs. S. Y. (No. 102387), Rh negative, with no antibodies, a 25-year-old gravida i, para 0, was admitted at term to our hospital at 8:00 P.M. on Feb. 19, 1952. Contractions were occurring about every 6 minutes. The position was left occipitoanterior, station plus 1, the cervix 50 per cent effaced and one finger dilated. The fetal heart tones were distinct, 148 per minute, in the left lower quadrant. At noon on the day of the admission there was a sudden gush of bright red amniotic fluid. The fetal heart tones became grossly irregular and apparently ceased. Immediate sterile vaginal examination showed the station to be at plus 1, the cervix 4 cm. dilated and quite thin. There was no evidence of placenta previa or abruptio placentae. By mere guess a diagnosis of vasa previa was made. At

2:30 P.M. an extremely pallid stillborn male infant was delivered. The umbilical cord contained little blood. Gross examination of the placenta showed a ruptured aneurysm of one of the major placental vessels leading to the cord. Gross and microscopic pathological examination (S-585-52) of the placenta showed a full-term placenta with a rupture of a small fetal vessel whose wall was incompletely developed (Fig. 1).

Vascular Rupture of a Velamentous Insertion of the Umbilical Cord.—

CASE 2.—Mrs. L. W. (No. 105797), Rh negative with no antibodies, a 39-year-old gravida ii, para i, at term, was admitted in active labor at 6:15 A.M. on April 22, 1952. At 10:15 A.M. the membranes ruptured and rectal examination showed the cervix to be fully dilated. The station was plus 1, and the position left occipitoanterior. There was a sudden gush of bright red blood and the fetal heart tones became grossly irregular. The patient was immediately prepared for delivery. Oxygen was started by mask and spontaneous delivery occurred at 10:28 A.M. The infant, a 9 pound female, appeared to be "white as a sheet" and was obviously in shock. Prompt examination of the cord and placenta showed a velamentous insertion of the cord with a rupture of the umbilical vein. Preparations for an immediate transfusion were instituted via the umbilical vein, using Type O Rh-negative (Witebsky treated) blood. A No. 17 polyethylene catheter was utilized. The response was dramatic and at the end of the transfusion the infant was pink and crying lustily. The child's postnatal course was entirely uneventful. The pathological diagnosis was (1308-52) reported as a very thin imperfectly developed wall of the umbilical vein with rupture (Fig. 2).

Velamentous Insertion of a Short Cord Wound Around the Neck With Rupture of One of the Umbilical Cord Vessels.—

CASE 3.—Mrs. B. A. (No. 114804), a 35-year-old gravida iii, para ii, was admitted in active labor at term at 9:30 P.M. on Oct. 8, 1953. The membranes had ruptured just prior to admission. The examination disclosed a frank breech position and the progress of labor was slow but steady. Around 1:45 A.M. on Oct. 9, 1953, the fetal heart tones were noted to have become irregular and they almost faded out with each pain. A diagnosis of cord compression was made and since, on sterile vaginal examination, the cervix was fully dilated, preparations for immediate delivery were made. Oxygen by mask was started and at 2:00 A.M. a breech extraction was done after a deep left mediolateral episiotomy. The cord was tightly wound around the neck and had to be clamped and cut before delivery could be effected. It was noted that the cord was extremely short. The child, a healthy-appearing male infant, cried at once. The placenta was spontaneously delivered at 2:06 A.M. Examination of the placenta and cord revealed a rupture of one of the major vessels leading to the cord with formation of a small hematoma, apparently between the layers of the membrane. Actually, the cord was not attached to the placenta but originated about 9 cm. out. It was felt that pull on a short cord brought about a rupture of one of these vessels. Fortunately, a hematoma formed and bleeding ceased. The pathological report (S-3292-53) supported this diagnosis. Mother and baby were discharged in excellent condition.

Summary and Conclusions

There is an apparent lack of interest in anemia of the newborn due to severe fetal blood loss during labor.

Three personal cases of intrauterine rupture of fetal vessels in labor have been presented. One infant died in utero, one was salvaged by immediate transfusion, and one required no special treatment. This condition is apparently not so rare as has been reported.

Evidence has been presented that, in the event of delivery of a shocked and pallid infant, prompt inspection of the cord and placenta is imperative.

The diagnosis actually depends on "a high index of suspicion." It is the immediate responsibility of the attending obstetrician to make the differential diagnosis of posthemorrhagic shock in the newborn.

Treatment consists of combating of shock by warmth, oxygen, and prompt replacement of blood loss by transfusion.

References

1. Torrey, W. E.: Am. J. Obst. & Gynec. **63**: 146, 1952.
2. Beer, D. C.: Obst. & Gynec. **3**: 595, 1954.
3. Rucker, M. P., and Tureman, G. R.: Virginia M. Monthly **72**: 202, 1945.
4. Groseclose, E. W.: Am. J. Obst. & Gynec. **61**: 80, 1951.
5. Fish, J. S., Bartholomew, R. A., Colvin, E. D., and Grimes, W. H.: Am. J. Obst. & Gynec. **61**: 20, 1951.
6. Wickster, G. Z.: Am. J. Obst. & Gynec. **63**: 524, 1952.
7. Kosmak, G. W.: Am. J. Obst. & Gynec. **16**: 438, 1928.
8. Leff, M.: Am. J. Obst. & Gynec. **22**: 117, 1931.
9. Busby, J. G., and Neal, R. F.: Am. J. Obst. & Gynec. **61**: 1173, 1951.

26 East Underwood Avenue

TERM PREGNANCY AND PROLAPSE OF THE CERVIX*

GRAYSON S. WALDROP, M.D., AND PAUL E. SIMPSON, M.D., RALEIGH, N. C.

PROLAPSE of the uterus during pregnancy has been reported 183 times in the literature. Nineteen of these cases have occurred in primiparas. The term "prolapsed uterus" appears to be a misnomer in most of the reported cases. Usually the problem is that of a cervix uteri that is tremendously increased in total mass although there may be some descensus of the body of the uterus also. Our experience with this condition in private practice has been limited to 2 patients. This is a report of 2 pregnancies occurring in one of these patients.

This 32-year-old white married gravida i, para 0, was seen for the first time on Aug. 19, 1950, when she presented herself for prenatal care and delivery. She had been married for seven years. Her past history disclosed no significant abnormality. The last menstrual period occurred on June 29, 1950, so that the expected date of confinement was April 6, 1951.

On pelvic examination the cervix was found to point slightly posterior, but no unusual impressions of the cervix were recorded at the time of this examination. The uterus appeared to be slightly enlarged, soft, and in neutral position. The clinical estimation was that of an average-sized gynecoid pelvis. The patient returned at regular intervals for prenatal care. Her weight at the beginning of pregnancy was 125 pounds and her total weight gain was 11 pounds.

On February 25, when approximately 34 weeks pregnant, she appeared in the office with the complaint that "something is hanging down between my legs." Examination disclosed a visible mass measuring approximately 8 cm. in length and 7 cm. in diameter. A diagnosis of hypertrophic, edematous, prolapsed cervix was made. No attempt was made to reposit the mass.

Additional rest in bed with the hips elevated was advised. For the next two weeks one hour of bed rest would suffice for the mass to disappear within the introitus where it would remain for two or three days. The patient attended to her general housework without difficulty. During the last month of pregnancy the cervical mass was prolapsed most of the time. Though bothersome, it was not incapacitating.

Labor began on March 9, 1951. Pelvic examination on admission revealed a cervical canal which admitted one finger with ease. The length of the canal was approximately 5 cm. The vertex was 2 cm. below the ischial spines and the mass protruded beyond the introitus. Cervical dilatation and effacement were slow but progressive. After approximately twenty-six hours of labor a considerable portion of the vertex was well outside the vagina with the suboccipiut at the lower margin of the symphysis. The cervix was approximately 7 cm. dilated with the rim of the cervix in plain view.

A saddle block was administered with the patient in the lateral prone position. After Dührssen's incisions had been made at 10 and 2 o'clock, spontaneous delivery occurred over a midline episiotomy. The infant was a full-term living female child weighing 7 pounds 6 ounces. The third stage of labor was normal. The episiotomy and Dührssen's incisions were repaired and the patient was returned to her room in good condition one hour following delivery with approximately 2 cm. of the cervix outside the vagina. The patient was placed on prophylactic penicillin for three days.

*Presented at the Seventeenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Virginia, Feb. 10, 11, and 12, 1955.

Her postpartum course in the hospital was afebrile. Prolapse recurred on the morning of the third hospital day following an enema. It disappeared shortly thereafter and did not recur. At the time of her examination at six weeks post partum the patient complained of a moderate amount of vaginal discharge. The cervix was approximately 5 cm. in length, larger than normal in diameter, and showed evidence of erosion.

The patient became pregnant again in 1953 and the expected date of confinement was recorded as March 16, 1954. Pelvic examination on her initial visit showed a uterus approximately twice the normal size and a cervix that was elongated and increased in diameter. Cervical erosion was present. Prolapse occurred six weeks earlier in the second pregnancy, i.e., at 28 weeks.

The patient adopted her former regime of utilizing bed rest with elevation of the hips for reduction of the prolapse. This was successful until the thirtieth week. During the next seven days, almost continuous bed rest failed to correct the condition. Hospitalization was recommended. She remained in the hospital for a period of eight days. The foot of the bed was elevated. Continuous hot wet dressings were applied to the cervix for six days.

During this period of prolapse we obtained Papanicolaou smears and two cervical biopsies were taken. It was hoped that the biopsy might throw some light on the mechanics involved in the etiology of this condition. The Papanicolaou smear was read as Type 2 negative for malignancy and was consistent with pregnancy. The report of the biopsy was as follows: In the several sections of cervical tissue examined, dilated lymphatics and veins, together with diffuse edema of tissue, were prominent. The surface included stratified squamous epithelium of the portio vaginalis and fundocervical mucosa, both of which showed changes of hyperplasia and hypertrophy, probably physiologic, and there was also physiologic hypertrophy of smooth muscle fibers. No actual proliferation of tissue representing a neoplasm was apparent, the changes described being interpreted as probably secondary to stasis. There was an inflammatory infiltrate of leukocytes limited to the superficial tissue of the mucosal surface.

On the seventh day of this hospital stay the cervix spontaneously receded within the vulva. Terramycin vaginal suppositories were inserted daily beginning on the seventh hospital day, and their use continued throughout her pregnancy. She was discharged improved without prolapse on the ninth hospital day. During the remainder of her pregnancy, prolapse was almost constant. The patient availed herself of increased rest in bed, but did a considerable portion of the cooking and housework.

Labor commenced at 2 A.M. on March 16, 1954. At the time of the admission at 6:10 A.M. the cervix was approximately 4 cm. dilated and 4 cm. in length. The cervix could be seen at the introitus, but was not prolapsed outside the vulva. The presenting part was on the pelvic floor. Labor progressed normally, under Trilene analgesia. At 7:30 A.M. a pudendal block was given and at 7:45 the suboccíput presented below the lower margin of the symphysis with approximately 3 cm. of the anterior lip of the cervix. The cervix was reduced by careful manual manipulation. Spontaneous delivery of a full-term living male child weighing 8 pounds 4 ounces was accomplished over a midline episiotomy at 7:51 A.M. The third stage of labor was uneventful. The duration of labor was approximately 6 hours. The vagina was packed. The vaginal pack was removed in 30 hours and the patient was out of bed on the second postpartum day. The prolapse recurred and persisted. Her postpartum course was otherwise uncomplicated and afebrile.

Spontaneous remission of the prolapse occurred two days before the patient's postpartum examination on May 10, 1954. The cervix was low lying in the vagina. The uterus was anteflexed, normal in size. There was no descensus except on traction of the cervix.

At the six months follow-up examination on Nov. 2, 1954, the cervix was approximately 5 to 6 cm. in length and 4 cm. in diameter, with evidence of misplaced endocervical tissue. No prolapse was evident. The vaginal muscle tone was considered poor. Vaginal exercises twice daily were recommened. No operation was contemplated at this time.

Original Communications

THE TREATMENT OF ENDOMETRIAL CARCINOMA BY MEANS OF REPEATED APPLICATIONS OF INTRACAVITARY RADIUM

WILLIAM J. DIECKMANN, B.S., M.D., CHARLES P. MCCARTNEY, B.S., M.D., AND J. W. J. CARPENDER, A.B., M.D., CHICAGO, ILL.

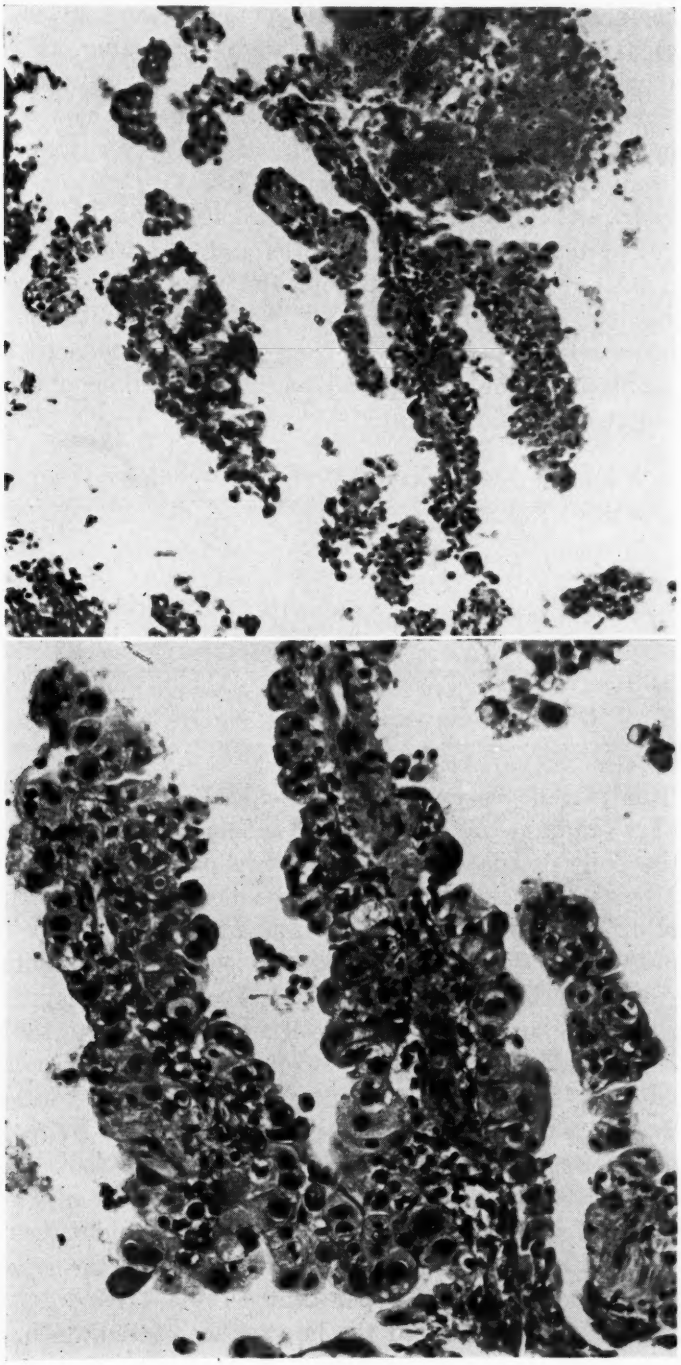
(From the Departments of Obstetrics and Gynecology and Radiology, the University of Chicago and the Chicago Lying-in Hospital)

SINCE 1931, it has been the departmental policy to treat all patients with carcinoma of the endometrium by means of intracavitary radium followed by a complete hysterectomy and bilateral salpingo-oophorectomy and the excision of a portion of the vaginal cuff, if the patient was considered to be a satisfactory surgical risk. If the patient was not a satisfactory operative risk, she received deep x-ray therapy to the parametria in addition to a single application of intracavitary radium. Prior to 1949, a central tandem and two lateral capsules were employed to administer 3,000 mg. hr. of intracavitary radium. Since 1949, a modification of Heyman's packing technique has been used, and the amount of radium which is employed has been increased to 5,000 mg. hr.

In 1942, a patient was referred to us with a diagnosis of endometrial carcinoma for which she had received 3,500 mg. hr. of intracavitary radium one month previously. This patient, who was 63 years of age, had a cerebral hemorrhage in 1941 with almost complete recovery. At the time of her admission to our hospital, she had a persistent blood pressure of 210/120 and presented evidence of cardiac failure. The medical consultant stated that this individual's maximum life expectancy was two years, and that she would not be suitable for surgery at any time. Furthermore, this patient had been treated with deep x-ray therapy in 1918 for metrorrhagia. As a consequence of this therapy, the lower half of the abdominal wall had sloughed, and a large hernia had developed. This had necessitated a hernia repair and skin grafting which had produced extensive scarring of the entire lower half of the abdomen. It was decided to recurette this patient, insert more radium, and to repeat this procedure at two- to three-month intervals until the curettings were negative. The operative procedures were carried out without difficulty under heavy morphine dosage. The first curettement was done one month following her initial treatment and showed the presence of an actively growing, poorly differentiated adenocarcinoma (Fig. 1). There was no clinical evidence of spread beyond the body of the uterus, which was enlarged to the size of a three months' gestation. An additional 2,400 mg. hr. of radium was administered at this time. Curettings obtained in three months were still suggestive of a malignancy, and 1,200 mg. hr. of radium was administered at this time for a total dosage of 7,100 mg. hr. Three months later, curettement was again performed but no tissue was obtained. The cervical canal was still patent fifteen months after the initial radium treatment. The patient lived for eight years after the diagnosis of carcinoma of the endometrium had been made and evidenced a clinical cure. She died in a nursing home at the age of 71 as a result of a cerebrovascular accident.

In the next few years, we had 5 patients with carcinoma of the endometrium which was limited to the body of the uterus who were considered unsuitable for surgery by our medical consultants because of severe cardiovascular disease,

A.



B.

Fig. 1.—R. H., No. 265778. *A*, Curettings showed persistence of an adenocarcinoma of the endometrium although the patient had been treated with 3,500 mg. hr. of intracavitary radium one month previously. She received an additional 2,400 mg. hr. of intracavitary radium at this time. *B*, Four months from the initial treatment, curettings still were suggestive of a malignancy and she was given an additional 1,200 mg. hr. of radium. During the first fourteen months there were two curettements in the hospital and two in the office. At the time of her death from a cerebral hemorrhage she presented no clinical evidence of malignancy.

and who were unacceptable to the roentgenologist for deep x-ray therapy because of their marked obesity. These patients were given the standard dose of intracavitary radium which we were employing at that time but recurettement was not carried out for the purpose of evaluating the effectiveness of this therapy. Within one to three years there was a local recurrence of the carcinoma in every instance and by then further treatment consisted of palliative radium therapy. As a result of this, we decided that we would periodically recurette all patients who had carcinoma of the endometrium which was limited to the body of the uterus and who were deemed unsuitable for operation by our medical consultants and who were unacceptable to our roentgenologists for deep x-ray therapy. We would administer supplemental amounts of intracavitary radium until the curettings evidenced no histological evidence of neoplasia or the patient had received the maximum dose of radium which we thought she could tolerate.

TABLE I. EXTENT OF MALIGNANCY

THERAPY	TOTAL CASES	Ca AT TIME OF SURGERY (PER CENT)	ENDOMETRIUM ONLY INVOLVED (PER CENT)	MYOMETRIUM AND ENDOMETRIUM INVOLVED. NO EXTENSION BEYOND (PER CENT)
Operation initial treatment	63	100	47.6	52.4
Radium followed by operation	42	57	14.0	43.0

During this period, we evaluated the effectiveness of a standard amount of intracavitary radium in eliminating endometrial carcinoma which was confined to the body of the uterus. Forty-two patients with endometrial carcinoma which was clinically confined to the body of the uterus were given 5,000 mg. hr. of intracavitary radium. The uteri were removed six to eight weeks later and were subjected to detailed histological examination. Forty-three per cent of these uteri presented no evidence of malignancy. Fourteen per cent had a persistence of the neoplasm which was confined to the endometrium, and 43 per cent evidenced neoplastic involvement of both endometrium and myometrium (Table I). Hence, this accepted therapeutic dose of 5,000 mg. hr. of intracavitary radium was inadequate in at least 57 per cent of the cases in which it was employed. In a concurrent control series of 63 uteri where no preoperative radium had been administered and in which the malignancy was confined to the body of the uterus, the endometrium alone was involved in 47.6 per cent and both the endometrium and the myometrium were involved by the neoplasm in 52.4 per cent (Table I).

Heyman[10] in 1927, emphasized the importance of radium in the treatment of endometrial carcinoma and reported a 44 per cent five-year survival in 46 cases of corpus carcinoma treated by intracavitary radium alone and a 60 per cent five-year survival in a selected group of 25 clinically operable patients who received the same treatment.

Reports by Healy and Cutler[8] in 1930, Burnam[3] in 1931, and Hurdon and Chambers[13] in 1933, on the combined use of radium and deep x-ray

therapy, confirmed Heyman's results. Subsequent reports have also confirmed Heyman's statements, and have discussed the variable effectiveness of intracavitary radium in the treatment of carcinoma of the endometrium. These reports have pointed out that the size of the uterus, distortion of the uterine cavity, and the anatomical extent of the carcinoma are factors influencing irradiation results.[4-7, 9, 11, 12, 14, 16-19, 22, 23]

Since endometrial carcinoma is treated blindly by the insertion of radium which one hopes will be in contact with the carcinoma, it is understandable why so many types of applicators have been devised to perfect this type of treatment. A comparison of various reports soon showed that where an adequate amount of radium had been used, and had been properly spread so that it covered as much of the surface of the uterine cavity as possible, the five-year survivals were improved.

Healy and Brown,[9] in 1939, reported an 85 per cent incidence of residual carcinoma in uteri when 1,200 to 2,700 mc. hr. of radon was administered prior to hysterectomy. But in those patients who had received 3,400 to 4,000 mc. hr., only 40 per cent showed residual carcinoma.

In 1943, Schmitz[20] reported that 6,000 mg. hr. of intracavitary radium administered in fractional doses by means of his Y applicator, and combined with deep x-ray therapy, resulted in the destruction of endometrial carcinoma in the 5 instances in which it was employed. This was in contrast to the persistence of the malignancy in 6 surgically removed specimens where irradiation was inadequate from the standpoint of the above criterion. In 1952, Schmitz and associates[21] reported that endometrial carcinoma was destroyed in 76 per cent of a series of 35 patients who were treated by preoperative irradiation therapy in accordance with their method. In this group of individuals who evidenced no malignancy in the removed uterus, the five-year survival was 87 per cent. In evaluating the factors influencing survival under these circumstances, these authors felt that the anatomical extent of the malignancy and the elimination of the neoplasm by preoperative irradiation therapy were the critical factors influencing survival in this combined method of therapy.

Arneson,[2] who has made extensive studies concerning the influence of preoperative irradiation upon survival of carcinoma of the uterine corpus, has reported that with carefully planned preoperative irradiation one can expect the disappearance of the neoplasm within the uterus in approximately three-fourths of all patients treated by this method and is of the opinion that the survival of these individuals in whom the malignancy is eliminated should be on the order of 85 per cent. He has stated that the principal factors affecting prognosis in carcinoma of the body of the uterus are the stage of advance of the malignancy, the size of the uterus, and the degree of differentiation of the tumor. He stated that, if any one of these factors is unfavorable, the probability of cure by hysterectomy alone is one in three but that preoperative irradiation will double the survival rate in this unfavorable group.

Since 1942, we have employed repeated curettage and multiple applications of intracavity radium as the sole method of therapy in 13 individuals with

endometrial carcinoma. Vascular-renal disease and obesity were contraindications to operation in 9 individuals, and arteriosclerotic heart disease associated with advanced age (70 years or over) precluded operative intervention in 4 individuals. In 12 individuals the malignancy was clinically confined to the body of the uterus. One individual presented a 5 cm. adnexal mass which was interpreted as representing an extrauterine extension of the malignancy. Deep x-ray therapy was contraindicated in 2 individuals because of an actinodermatitis resulting from its previous use for benign conditions and the employment of external irradiation was considered inadvisable by the roentgenologist in the remainder because of marked obesity.

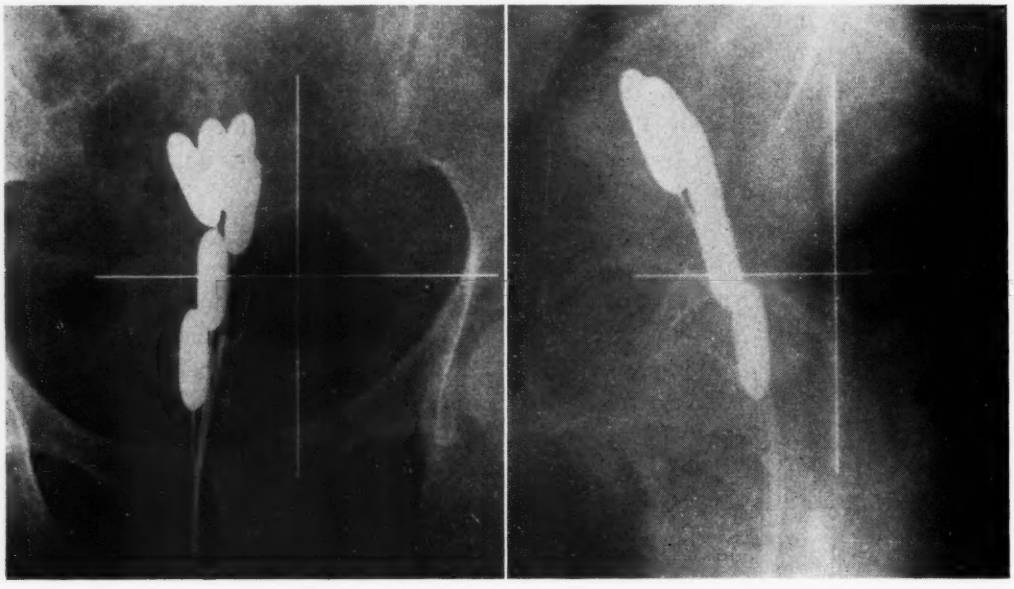


Fig. 2.—A. Z., No. 478149, aged 64 years. The patient was considered to be medically inoperable. Figures show anteroposterior (*A*) and lateral (*B*) roentgenograms of pelvis, illustrating position of multiple sources of radium. The uterus was 8 cm. in depth and the uterine cavity accommodated five radium capsules, each of which contained 10 mg. of radium. A sixth capsule which contained no radium was placed in the cervical canal to maintain patency of that structure in order to facilitate periodic recurettement. This patient received 4,800 mg. hr. of radium initially, and 3,000 mg. hr. of radium five months later for a total dosage of 7,800 mg. hr. She has survived for six and one-half years with no evidence of malignancy.

Method of Treatment

The administration of fractional doses of intrauterine radium was the sole method of therapy employed in the treatment of these individuals. From 1942 to mid-1949, inclusive, three sources of radium were utilized. These consisted of a central tandem containing from 25 to 35 mg. of radium, which extended from the internal cervical os to the fundus, and a total of two lateral capsules, each of which contained either 5 or 10 mg. of radium. The total amount of radium employed varied from 45 to 55 mg. The amount of filtration was equivalent to 2.0 mm. of platinum. The initial amount of radium administered under these circumstances varied from 3,500 mg. hr. to 5,760 mg. hr. This was a departure from the 3,000 mg. hr. which we customarily employed when administering intracavitary radium by this method. The amount of radium contributed from each source varied from 960 to 2,400 mg. hr.

From the middle of 1949, a packing technique adapted from that employed by Heyman[11, 12] was used. With this method the uterine cavity was packed with multiple, small, olivelike capsules. The filtration was 2.0 mm. of platinum. The amount of radium employed varied from 40 to 105 mg., and the initial dose ranged from 3,900 to 5,000 mg. hr. The amount of radium contributed from each source varied from 350 to 1,200 mg. hr. In an attempt to ensure the patency of the cervical canal and thus facilitate periodic post irradiation curettement, a vaginal plaque was not employed and a dummy was placed within the cervical canal each time that radium was administered (Fig. 2).

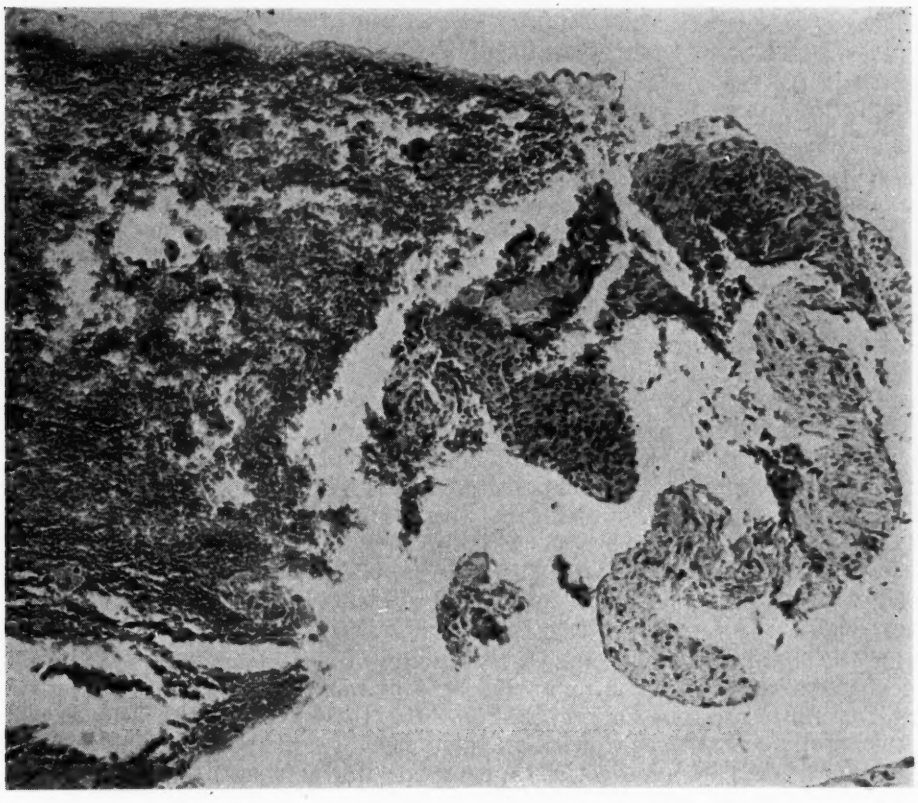


Fig. 3.—S. S., No. 414579. Low power of curettings obtained three months after the administration of 5,000 mg. hr. of intracavitary radium. Although there was no evidence of malignancy, the patient received an additional 1,620 mg. hr. of intracavitary radium which resulted in a total dosage of 6,200 mg. hr. This patient has survived for eight years with no evidence of malignancy.

The uterus was recuretted in all 13 cases at intervals which varied from one month to 30 months from the time of initial therapy. The patients' failure to return at the designated time was responsible for those instances where the intervals exceeded three months. In 11 instances, the histological finding of endometrial carcinoma was an indication for the administration of additional intracavitary radium. In 2 instances additional radium was administered although the persistence of the carcinoma could not be demonstrated (Fig. 3). The amount of radium employed in these 13 cases at this second application varied from 1,200 to 3,000 mg. hr., with a contribution from each source of from 240 to 1,200 mg. hr. A second recurettement with a time interval varying from four to forty-one months from the time of initial

therapy was done in 11 instances with the administration of additional radium in 7 cases. The dose of radium in these cases varied from 810 to 1,500 mg. hr. The contribution from each source varied from 240 to 800 mg. hr.

Curettage was repeated for the third time in 5 individuals. None of these individuals received a fourth application of radium.

The total amount of radium administered varied from 5,490 to 9,200 mg. hr. in these 13 individuals. Five individuals were treated by means of a tandem and two capsules, as previously described. Two individuals were treated initially by use of the tandem but received their subsequent irradiation by means of the packing technique, and 6 individuals were treated solely by the packing technique (Table II).

Results of Treatment

Survival.—

Nine of the 13 patients who comprised this series are living. Two individuals died as a result of their malignancy. The interval between initial treatment and death was four years in each of these cases. Both individuals were treated by means of the tandem and two capsules as outlined previously, and both had two repeat curettements which in each instance revealed the persistence of their malignancy. One individual had an adenoacanthoma. The other patient had a poorly differentiated adenocarcinoma. Both received two applications of radium following their initial therapy. The total amount of radium administered in the 2 cases was 7,600 and 8,980 mg. hr., respectively. At the time of initial therapy, one of these individuals evidenced a 5 cm. left adnexal mass which was interpreted as representing an ovarian metastasis from the endometrial carcinoma. The third death was due to heart disease and was unrelated to this patient's malignancy. This individual died three years after therapy had been instituted and presented no evidence of malignancy at autopsy. The fourth death was the result of a cerebrovascular accident which occurred at the age of 71 in a patient whose life expectancy at the time of initial treatment was stated to be two years. This patient survived for eight years and presented no clinical evidence of malignancy at the time of her death.

Of the 9 surviving patients, 8 are living with no evidence of malignancy. Five of these individuals have survived for five or more years. Two have survived for four and one-half years, one for three years, and one has lived for two and one-half years with no evidence of carcinoma. One individual who was 74 years of age at the time of her initial therapy has survived for twenty-five months with a persistence of her malignancy for which she received a third application of radium in the amount of 1,950 mg. hr. during the period in which this paper was written. This additional radium has brought the total amount of intracavitary radium which this patient has received to 8,190 mg. hr. (Fig. 4, *A* to *E*). She is clinically well at four years.

There were 3 adenoacanthomas, 3 well-differentiated adenocarcinomas, 4 intermediate adenocarcinomas, and 3 poorly differentiated adenocarcinomas in this series. Of the patients who died of their malignancy, one had an adenoacanthoma and the other a poorly differentiated adenocarcinoma.

The size of the uterus in these 13 patients varied from normal to that of a three months' gestation. The degree of uterine enlargement in the two individuals who died as a result of the persistence of malignancy was that of a one and one-half months' and a three months' gestation, respectively. In the 3 six-year survivals, the size of the uterus was normal in one, one and one-half months in one, and two months in the third. In the remaining 8 individuals, the size of the uterus varied from normal to that of a three months' gestation. This information is presented in Table I.

Nine patients, or 69 per cent of this series, are eligible for five-year survival. Two of these died from intercurrent disease after surviving for three years and eight years, respectively, and presented no evidence of malignancy at the time of their deaths. Two of these individuals died from endometrial carcinoma. The uncorrected five-year survival rate is 67 per cent. The corrected five-year survival rate in this group is 75 per cent.

Complications of Irradiation Therapy.—

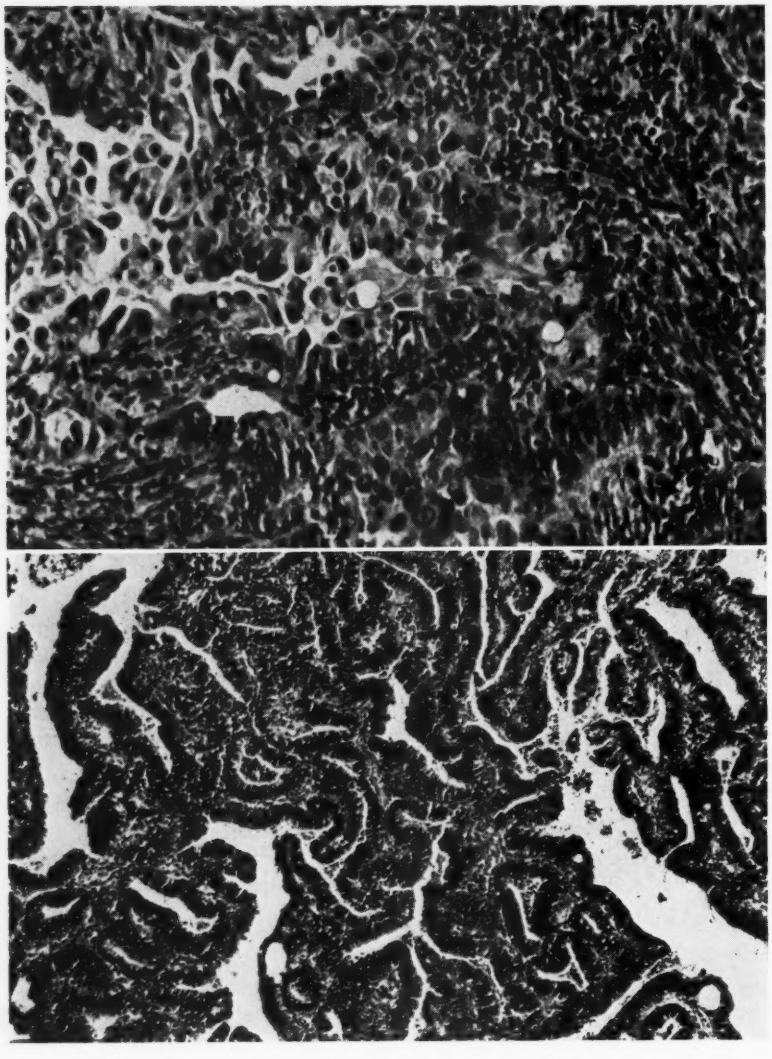
None of the major visceral complications peculiar to irradiation therapy occurred in this group. Minor abnormalities occurred in 3 individuals. Two of this group manifested bowel distress, which subsided without sequelae. One of these patients who had been treated by the packing technique experienced rectal tenesmus and diarrhea following the administration of 2,000 mg. hr. of radium at the time of her second curettement. She had received 4,000 mg. hr. of radium six months previously. The second application of radium consisted of four 10 mg. capsules which were left in place for 50 hours. The second patient, who also was treated by the packing technique, developed transient bowel distress, following a total radium dosage of 5,490 mg. hr. The bowel distress in this instance appeared when a second application of 1,500 mg. hr. of radium was administered by means of twelve 5 mg. capsules for a period of twenty-five hours. This radium was administered twelve months after her initial treatment. Pyometra occurred in one individual who was treated by the tandem technique. This manifested itself after three applications of radium during a forty-one-month period. The total dose in this instance was 8,948 mg. hr. This individual died of malignancy after surviving four years. The only instance of vaginal metastases in this series occurred in this patient whose neoplasm was classified as an adenoacanthoma. These metastases occurred after the administration of 8,938 mg. hr. of radium and appeared seven months before her death, and forty-one months after her initial treatment.

It is interesting to note that in 10 cases, or 77 per cent of the series, over 7,000 mg. hr. of intrauterine radium was administered in fractional doses without producing significant irradiation injury and in 4 cases, or 31 per cent of the series, 8,000 to 9,200 mg. hr. of radium was administered without complication (Table II).

Persistence of Malignancy.—

Only 2 patients, or 15 per cent of this series, presented no evidence of malignancy upon being curetted following initial applications of radium in the amounts of 4,000 to 5,000 mg. hr., respectively. These individuals were treated by the packing technique. One uterus was of normal size. The neoplasm in this instance was classified as an adenoacanthoma. The second uterus was enlarged to the size of a six weeks' gestation and the malignancy was classified as a poorly differentiated adenocarcinoma. Carcinoma persisted in 11 individuals, or 85 per cent of the series, after initial amounts of radium which varied from 3,500 to 5,760 mg. hr. In this group, negative curettings were obtained in 4 patients after the administration of additional amounts of from 1,500 to 3,000 mg. hr. of radium with total doses of from 5,490 to 7,800 mg. hr. On the other hand, endometrial carcinoma was still present in 7 individuals, or 54 per cent of the total series, after the administration of supplemental radium in amounts of from 1,680 to 2,640 mg. hr., with total individual combined dosages which varied from 6,000 to 8,000 mg. hr. The average interval between applications was five months with one instance in which a thirty-one-month period elapsed before a second application of radium was made because of the patient's failure to return at the designated time.

A.



B.

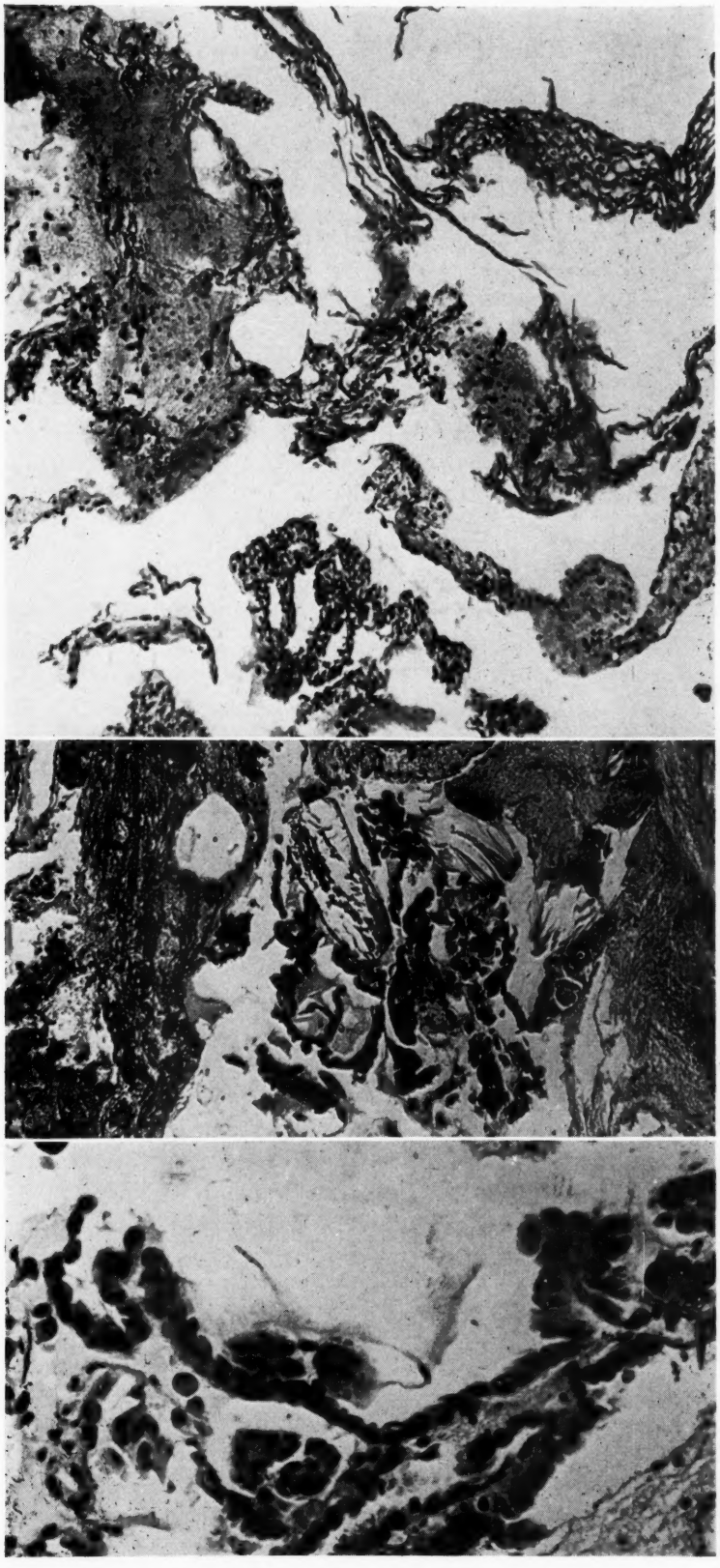
Fig. 4.—S. M. The patient had had postmenopausal bleeding of seven months' duration. The uterus was enlarged to the size of a ten weeks' gestation and was sounded to 10 cm. There was no clinical evidence of extrauterine spread of the malignancy.

A, High power of curettings of an endometrial carcinoma. The uterus was packed with 6 capsules, each of which contained 10 mg of radium, by which 4,800 mg. hr. was administered.

B, Curettings showing a persistence of the malignancy were obtained five months after administration of 4,800 mg. hr. of radium. Supplemental radium in the amount of 1,440 mg. hr. was administered by packing the uterus with 6 capsules, each of which contained 10 mg. of radium. The resulting total dose of radium was 6,200 mg. hr.

C, Curettings obtained three months after the administration of 1,440 mg. hr. of supplemental intracavitary radium for a total dosage of 6,200 mg. hr. No evidence of malignancy is present.

D and *E*, Curettings obtained two years after the initial treatment and seventeen months after the previous curettement (*C*) show a persistence of the malignancy after the administration of 6,200 mg. hr. of intracavitary radium. This patient was given an additional 1,950 mg. hr. of intracavitary radium for a total dosage of 8,190 mg. hr. The effectiveness of this recent additional amount of radium has not been determined.



C.

D.

E.

Fig. 4, *C, D,* and *E.—For legend see opposite page.*

TABLE II. OUTLINE OF 13 CASES

PATIENT	AGE	UTERUS: SIZE (COMPARABLE TO MONTHS OF GESTATION)	UTERUS: DEPTH (CM.)	NEOPLASM	NUMBER REPEAT D & C (TIME = FROM INITIAL THERAPY)	RADIUM*: INITIAL (MG./HR.)	RADIUM*: REPEAT (MG./HR.)	RADIUM*: TOTAL (MG./HR.)	SURVIVAL IN YEARS WITH OR WITHOUT CA PRESENT (TO SEPT. 30, 1955)
F. H.	51	1½	9	Well-differentiated adenocarcinoma	2— 3 mo.—CA 9 mo.—CA	4,500—T	2,017 3 mo.—T 810 9 mo.—T	7,327	No CA 8½ years
N. S.	76	2½	10	Well-differentiated adenocarcinoma	2— 3 mo.—CA 9 mo.—No CA	5,760—T	2,012 3 mo.—T	7,772	No CA 8 years
S. S.	60	1½	8	Poorly differentiated adenocarcinoma	1— 3 mo.—No CA	5,000—T	1,620 3 mo.—T	6,620	No CA 8 years
F. J.	54	2	9	Intermediate adenocarcinoma	3— 3 mo.—CA 10 mo.—CA 28 mo.—No CA	5,280—T	1,680 3 mo.—T 2,000 10 mo.—O	8,960	No CA 6½ years
A. Z.	64	Normal		Intermediate adenocarcinoma	2— 3 mo.—CA 5 mo.—No CA	4,800—O	3,000 3 mo.—O	7,800	No CA 6 years
L. J.	74	1½	8	Intermediate adenocarcinoma	2— 2 mo.—CA 7 mo.—CA	5,000—T	3,000 3 mo.—O 1,200 7 mo.—O	9,200	No CA 2½ years
E. M.	60	2½	9.5	Well-differentiated adenocarcinoma	2— 3 mo.—CA 12 mo.—No CA	3,990—O	1,500 —O	5,490	No CA 4½ years
L. V.	59	Normal	5	Intermediate adenocarcinoma	3— 3 mo.—CA 5 mo.—CA 6 mo.—CA	5,000—O	1,800 5 mo.—O 1,200 6 mo.—O	8,000	No CA 4½ years
S. M.	74	2½	10	Adenoacanthoma	3— 5 mo.—CA 8 mo.—No CA 25 mo.—CA	4,800—O	1,440 5 mo.—O 1,950 25 mo.—O	8,190	No CA 4 years
M. Bo.	67	1½	9	Poorly differentiated adenocarcinoma	2— 7 mo.—CA 26 mo.—CA	4,320—T	1,680 7 mo.—T 1,600 26 mo.—T	7,600	Died. CA 4 years Vaginal metastases
M. B.	70	3 Left adnexal mass X-ray menopause Actinodermatitis	11	Adenoacanthoma	2—30 mo.—CA 41 mo.—CA	4,800—T	2,640 3 mo.—T 1,608 41 mo.—T	8,948	Died CA 4 years
M. C.	63	Normal	8	Adenoacanthoma	1— 6 mo.—No CA	4,000—O	2,000 —O	6,000	Died heart disease 3 years. No CA
R. H.	63	3 X-ray menopause Actinodermatitis	14	Poorly differentiated adenocarcinoma	4— 1 mo.—CA 4 mo.—CA 7 mo.—No tissue 11 mo.—No tissue	3,500—T	2,400 1 mo.—T 1,200 4 mo.—T	7,100	Died cardiovascular accident, 8 years No CA clinically

*T = Tandem.
O = Olives.

After an interval of from three to twenty-five months, 7 patients received a second supplementary application of radium in amounts which varied from 810 to 1,600 mg. hr. This resulted in the clinical elimination of the neoplasm in 5 individuals. These latter individuals received a total of from 7,100 to 9,200 mg. hr. of radium. Three of these individuals constitute five-year survivals, and 2 survived for four and one-half years. Carcinoma persisted in 2 individuals after a second supplementary application of radium in amounts of 1,600 and 1,500 mg. hr. and total radium dosages of from 7,600 to 8,948 mg. hr., respectively. These patients succumbed to the malignancy after surviving four years. One of them presented clinical evidence of extrauterine extension of the neoplasm at the time of initial therapy.

The status of the remaining individual in this group is questionable, owing to the fact that less than one year has elapsed since the administration of a second supplementary dose of radium. This case is of interest since recurettement three months following the second administration of radium disclosed no evidence of malignancy, yet actively growing carcinoma localized in the region of the right cornu was present on recurettement seventeen months later (Fig. 4, *C*, *D*, and *E*).

Comment

The anatomical extent of the malignancy, the size of the uterus, and the method of therapy are critical factors influencing survival in carcinoma of the uterine corpus. In our experience, the employment of adequate surgery in the treatment of this malignancy when it is limited to the body of the uterus has resulted in an 85 per cent five-year survival rate.[15] This is in contrast to a 47 per cent five-year survival rate in 24 per cent of our patients in whom the anatomical extent of the malignancy was favorable but who were treated by a single application of from 3,000 to 5,000 mg. hr. of intracavitary radium combined with maximum deep x-ray therapy. As a consequence of this therapy, the high rate of curability inherent in endometrial carcinoma of limited anatomical extent was not realized in this group of patients. Uncorrected and corrected five-year survival rates of 69 per cent and 75 per cent, respectively, in the cases which we have just reported suggest that repeated postirradiation curettage at two- to three-month intervals for the purpose of the early detection of a persistence of the malignancy and the administration of supplemental intracavitary radium to the limit of individual tolerance in the presence of continued neoplastic activity affords a means for increasing the survival rate in this statistically significant group of individuals. We feel that this approach to the problem of medically inoperable corpus carcinoma is preferable to delaying supplementary radium therapy until clinical recurrence is obvious and only palliation can be expected from its use.

Our experience indicates that from 8,000 to 9,000 mg. hr. of intracavitary radium can be tolerated when administered by the methods outlined and under the conditions which have been presented. We believe, therefore, that when intracavitary radium alone is used in the treatment of persistent endometrial carcinoma under the circumstances outlined, the administration of supplemental amounts of radium up to 9,000 mg. hr. is indicated if curettage discloses a persistence of the malignancy.

Although we did not employ an intravaginal source of radium in these 13 patients, we now include its use at the termination of radium therapy. Similarly, we utilize a vaginal plaque to administer approximately 2,400 mg. hr. of radium in a single dose to the vaginal vault where operation has been employed in the treatment of endometrial carcinoma but where preoperative intracavitary radium was not administered.

We realize that the excessive uterine manipulation incidental to repeated curettements is likely to cause a spread of carcinoma. However, the postoperative mortality after hysterectomy in the elderly patients who are considered poor operative risks for various reasons is extremely high.

Summary

Thirteen individuals with endometrial carcinoma were treated by repeated applications of intracavitary radium alone. The medical status of these patients precluded major surgery and they were unacceptable to the roentgenologist for deep x-ray therapy because of obesity or because they had previously been treated by x-ray for benign conditions.

It was found that this method of therapy significantly increased the survival rate in these individuals, and that fractional doses of intracavitary radium in total amounts of 9,000 mg. hr. could be employed under the conditions which were presented without significant irradiation injury.

Sixty-seven per cent of these patients are eligible for five-year survival. The uncorrected and corrected five-year survival rates are 67 and 75 per cent, respectively.

Our study, along with several others, shows that a standard dose of intracavitary radium will not destory all carcinoma cells if the uterus is large or the malignancy is extensive.

References

1. Arneson, A. N., Stanko, W. W., and Nolan, J. F.: Am. J. Obst. & Gynec. **55**: 64, 1948.
2. Arneson, A. N.: Bull. New York Acad. Med. **29**: 395, 1953.
3. Burnam, C. F.: Ann. Surg. **93**: 436, 1931.
4. Crossen, H. S.: J. Missouri M. A. **37**: 376, 1940.
5. Donovan, M. S., and Warren, S.: Surg., Gynec. & Obst. **74**: 1106, 1942.
6. Friedman, M.: Radiology **35**: 28, 1940.
7. Gray, L. A., Friedman, M., and Randall, W. S.: Surg., Gynec. & Obst. **82**: 386, 1946.
8. Healy, W. P., and Cutler, M.: Am. J. Obst. & Gynec. **19**: 457, 1930.
9. Healy, W. P., and Brown, R. L.: Am. J. Obst. & Gynec. **38**: 1, 1939.
10. Heyman, J.: Acta radiol. **8**: 363, **1927.**
11. Heyman, J.: Acta radiol. **16**: 129, 1935.
12. Heyman, J.: J. A. M. A. **135**: 412, 1947.
13. Hurdon, E., and Chambers, H.: Proc. Roy. Soc. Med. **26**: 710, 1933.
14. Javert, C. T., and Hofman, K.: Cancer **5**: 485, 1952.
15. McCartney, C. P.: S. Clin. North America **33**: 241, 1953.
16. Nolan, J. F., and Steele, J. P.: Radiology **51**: 166, 1948.
17. Sampson, J. A.: Am. J. Obst. & Gynec. **28**: 783, 1934.
18. Scheffey, L. C., Thudium, W. J., and Farell, D. M.: Am. J. Obst. & Gynec. **52**: 529, 1946.
19. Schmitz, H., and Schmitz, H. E.: Am. J. Roentgenol. **34**: 749, 1935.
20. Schmitz, H. E., Sheehan, J. F., and Towne, J.: Am. J. Obst. & Gynec. **45**: 377, 1943.
21. Schmitz, H. E., Smith, C. J., and Gajewski, C. J.: Am. J. Obst. & Gynec. **64**: 952, 1952.
22. Stowe, L. M.: Am. J. Obst. & Gynec. **51**: 57, 1946.
23. Taylor, H. C., and Becker, W. F.: Surg., Gynec. & Obst. **84**: 129, 1947.

VAGINAL FUNGI AND THEIR RELATION TO SPERM SURVIVAL*

G. E. Seegar Jones, M.D., John L. Wood, Ph.D., David W. Bishop, Ph.D., and Robert S. Donoho, M.D., Baltimore, Md.

(From the Departments of Gynecology and Medicine, Johns Hopkins Hospital and University and the Department of Embryology, Carnegie Institute of Washington, Baltimore, Maryland)

OUR interest in vaginal fungi was first aroused by the detection of *Candida krusei* in the vaginas of two patients who complained of infertility. Both of these women had immobile sperm in the vaginal fluids and cervical mucus even in the preovulatory and ovulatory phases of their cycles. Both became pregnant after elimination of the *C. krusei* from the vagina. In order to determine the relative frequency of the *C. krusei* as well as to record other types of fungi which might be encountered in the vagina, cultures were taken from 124 private gynecological patients. The clinical pathogenicity of the various fungus strains and the effect of these organisms upon sperm survival were also studied.

In a brief review of the literature it can be determined that the species *C. krusei* was originally isolated by Castellani[1] in 1910. Plass and associates[2] in their classic work described 39 strains of Monilia obtained from vaginal secretions. Krusei was isolated from 6 patients in this series, 4 with and 2 without vaginitis. Lamb and Lamb[3] in 1935 stated that krusei is different from other Candida and is seldom isolated from human sources. Martin and co-workers[4] in 1937 reported four strains of *C. krusei* among 59 Candida isolated from the vagina and Schnoor[5] in 1939 isolated 18 krusei in a total of 108 Candida from 314 stool specimens of apparently normal people.

Material

One hundred and sixty vaginal cultures were taken from 124 consecutive patients. Twenty-one of these women complained of pruritus or leukorrhea, and these patients were classified as symptomatic. The remaining 102 women, when specifically questioned about such symptoms, had no complaints involving the vagina or vulva. These patients were classified as asymptomatic.

Mycological Techniques and Classifications

The standard isolation medium used was beef extract-peptone-glucose-tartaric acid agar. This medium is prepared by melting 10 ml. of Difco nutrient agar, and adding 0.5 ml. of a solution containing 50 per cent glucose and 5 per cent tartaric acid. This medium, which contains a final concentration of about 5 per cent glucose and 0.5 per cent tartaric acid, prevents the growth of most bacteria and yet allows good growth of most yeasts and molds.

Fungi were divided into four groups according to their cultural characteristics: (1) Candida species, (2) *C. albicans,* (3) *C. krusei,* and (4) yeast not Candida.

*This study was made under a grant from the Robert L. Dickinson Memorial Fund, Planned Parenthood Federation of America, Inc.

Yeasts isolated on glucose-tartaric acid slants were grown for two days at 37° C. in glucose-peptone broth in order to check for pellicle formation. One- to two-day-old pure cultures were cut into corn meal agar. If mycelium and blastospores were formed, the organism was considered to be a Candida species. If in addition, chlamydospores were formed, the culture was considered to be *Candida albicans.*

The oval to cylindrical cells, flat dry colonies, formation of a pellicle on broth, and fermentation of glucose only, made *C. krusei* easier to recognize than some other species of Candidi. Mycelium, however, may sometimes be formed with difficulty and a worker may not at first realize that he is dealing with a Candida.

Yeasts which did not form mycelium in corn meal agar were listed as yeast not Candida. Filamentous fungi which were occasionally isolated were excluded in this study as air or wood contaminants.

Parakrusei and tropicalis, described by Martin and Jones,[6] would come under Candida species in this classification while stellatoidea could be classified as a *Candida albicans.* This may account for the one instance of an asymptomatic *Candida albicans* in the present series.

In order to check the cultures for pathogenicity, 0.1 ml. of a heavy suspension of yeast cells in physological saline (incubated for 2 days at 37° C. on glucose-peptone broth) was injected intravenously into the tail vein of white mice. Mice were observed over a six-week period and their weights recorded. If the animals were still alive at the end of the observation period they were autopsied and organs were cultured for fungi.[7]

Observations

Results of Fungus Cultures on 21 Symptomatic Patients.—Fourteen of the 21 symptomatic patients were found to have positive fungus cultures and 7 had negative. Ten of the positive cultures were identified as *Candida albicans,* but 4 were identified as a fungus other than *C. albicans;* of these four cultures, two belonged to the genus Candida, (not *C. albicans*) and two did not. Repeated vaginal cultures from all patients demonstrated the same organism as was originally isolated.

The 7 patients with negative cultures were further investigated. Four of these women were found, by salt solution examination, to have a Trichomonas infection. One patient was found to have cystitis and trigonitis and when the bladder infection was relieved her vaginal symptoms disappeared. Another of these 7 patients had subsequent cultures taken six months later, and these showed a fungus other than *C. albicans.* The seventh patient had a vaginitis of undetermined etiology.

Vaginal Fungus Cultures Among Asymptomatic Patients.—Thirteen positive fungus cultures were isolated from the 102 women who were judged asymptomatic. Only one of these cultures was identified as *C. albicans.* Its pathogenicity was further studied by mouse inoculation. Since it was found to produce death of the mouse, this should have been, according to the usual criteria, a pathogenic fungus. Two cultures were identified as Candida, but not *C. albicans,* and 3 were identified as a genus other than Candida. Two patients repeatedly had cultures of *C. krusei,* and 5 had cultures of yeast which were unidentified. Only 5 of the cultures were repeated in this group of patients but in every instance the same organism was present.

Sperm Survival

Only one organism, *Candida krusei,* in our series seemed to affect sperm survival or motility in the vaginal vault and in cervical mucus. In 2 patients

in whom *C. krusei* was repeatedly found the preovulatory, postcoital examination for motile sperm was negative as early as two hours after intercourse. Although large numbers of sperm were present in cervical mucus, none were motile. The observation was confirmed on repeated menstrual cycles.

The presence of fungus in the cervical mucus after intercourse was confirmed by microscopic examination. This was possibly due to a mechanical factor rather than actual growth of fungi in the cervical mucus, as samples of mucus examined at other times were often free of organisms and cultures of mucus showed a very low colony count as compared to vaginal cultures.

In vitro investigations failed to disclose spermicidal activity of the fungus, indicating no direct inhibitory effect. It was therefore thought that the reduction in sperm motility might be produced by a competitive action of the fungus with sperm for some essential substrate in the cervical mucus.

Since the *C. krusei* had been found to be asymptomatic in 3 patients, and since when inoculated into mice it failed to produce illness or death, this fungus was considered nonpathogenic. We were therefore encouraged to try transplantation by inoculation technique in an effort to investigate further the spermicidal activities of *C. krusei.* Although Salvin[8] reports a strain of *C. krusei* to be relatively virulent in mice, we obtained this strain from him and, when living cells were injected into mice by our method for checking pathogenicity of strains of Candida, the mice were apparently unaffected.

Inoculation Experiments

Vaginal inoculations of *Candida krusei* were made in 27 patients, and the fungus was recovered from the vagina of these patients in every instance. However, the duration of survival of the fungus in the vagina showed marked variations. After vaginal inoculation, cultures taken every few hours showed consistently decreasing numbers of fungus colonies during the first 48 hours, shortly after which time the majority of cultures became sterile. Rarely was a fungus recovered four days after inoculation, although one woman who had uncontrolled diabetes maintained the culture of *C. krusei* for a seven-month period. The other patients all failed to maintain cultures after a menstrual period. Inoculations were made on 2 women twice a week throughout one month in order to determine if the phase of the menstrual cycle might influence the ability of the vagina to maintain a fungus culture. No differences were observed for the menstrual phase in the 2 patients studied. No symptoms were produced by the fungus in any of the women who carried *C. krusei,* indicating again that this fungus, at least of the strain used, was nonpathogenic.

It was surprising that the inoculated cultures lived in the vagina for such a short time, three days being the average, with eight days the longest survival time except for the one diabetic patient. Techniques were then sought to elucidate this finding. Since fungus vaginitis is prone to occur in three clinical conditions, we decided to investigate the possibility of inoculation under these conditions—diabetes, pregnancy, and antibiotic therapy. Three diabetic patients were inoculated with *C. krusei.* One, who consistently showed an elevated blood sugar, maintained a positive culture, after a single inoculation, during a seven-month period. Two patients with well-controlled diabetes failed to maintain cultures. Five pregnant women were inoculated. The cultures were not maintained in any of these patients. Aureomycin suppositories of 250 mg. were used daily for four days prior to fungus inoculation and four days thereafter in 6 patients. By this technique the fungus survival time was usually prolonged, and in one instance it was maintained for two weeks at which time a menstrual period ensued. The culture taken postmenstrually was sterile, and this was repeatedly confirmed.

The experiments indicate that, at least for nonpathogenic types of fungus, some factor other than the mere exposure to the fungus itself is necessary for a continued survival of the organism in the vagina. The absence of bacteria in the vagina is apparently an important factor since Aureomycin suppositories allow the maintenance of vaginal fungus. The bacterial exudates in the vagina are apparently not responsible for this inhibitory action, since plates of fungus streaked with vaginal secretions show no inhibition of growth.

In 10 of the 27 patients inoculated with *C. krusei,* vaginal cultures were maintained for long enough periods of time to test sperm survival. All 10 patients with positive krusei cultures had immotile sperm in the cervical mucus during the preovulatory phase of the cycle and within 12 hours after intercourse. Postcoital sperm survival tests in these patients before and after positive *C. krusei* cultures were obtained had been satisfactory. All the patients studied complained of infertility, however, and thus cannot be considered normal women.

In a further effort to elaborate this finding, 17 monkeys (*Macaca mulatta*) were inoculated vaginally with the *C. krusei.* It was found, as had been demonstrated in women, that cultures could not be maintained in the monkey vagina, without the use of Aureomycin. All 17 monkeys were inoculated on two occasions at 48 hour intervals and recultured five and seven days after the second inoculation. All 17 monkeys showed sterile vaginal cultures at the end of this period. Six monkeys were given 250 mg. of Aureomycin daily by stomach gavage for four days prior to vaginal inoculation and four days after inoculation. All of these monkeys maintained a *C. krusei* in the vagina for at least an eight-day period. The culture could usually be maintained as long as the Aureomycin was given. Vaginal suppositories of Aureomycin, 50 mg., were administered to 4 animals four days before and after vaginal inoculation with *C. krusei,* but only one culture was maintained by this method.

The monkey was unsuitable for sperm-survival tests, since the postcoital vaginal plug, in which sperm rapidly lose motility, precludes the free exposure of the cells to the vaginal fluids. Although the fungus may have decreased the survival time of free sperm in the vagina to a degree, the fungus did not show an immediate spermicidal effect. One animal which showed a very slight growth of *C. krusei* when mated became pregnant, but 3 others which were mated did not. Because of the variability in mating monkeys successfully, the failure of these 3 to become pregnant could not be attributed to the fungus infestation.

Comment

The findings tend to confirm the general clinical impression that *C. albicans* is usually pathogenic for women as well as for mice and is the most common pathogenic type of fungus infection encountered in the vagina. However, this fungus can apparently occur occasionally in the absence of symptoms as 10 of 11 patients with positive cultures of *C. albicans* had associated vaginal symptoms but one professed to be asymptomatic. Other strains of fungus may also be pathogenic in women since both Candida species and yeast other than Candida produced symptoms of vaginitis four times in the present series. Two patients who showed *Candida krusei* were consistently asymptomatic, and a third patient who is not included in this series was also asymptomatic. *Candida krusei* therefore has been judged to be usually nonpathogenic in the human vagina.

Although the results of the spermicidal effects of *C. krusei* in the vaginas of women are meager, and those in the monkey are not positive, there is a definite indication that sperm survival in the cervical mucus is incompatible with the growth of the fungus. This incompatibility may be attributed to the competition of spermatozoa with the fungus for metabolic substrates. A direct inhibitory effect appears to be excluded by the negative in vitro studies. In those instances in which Aureomycin had been administered to facilitate fungus growth, the resulting spermicidal action may have been due to the antibiotic itself or to the combined inhibition of antibiotic and fungus. According to the findings of Buxton,[9] a spermicidal effect shown by several antibiotics may be correlated with the intensity of yellow pigmentation. Aureomycin, therefore, may well possess a sperm-killing capacity not necessarily related to its antibiotic property. If further work can establish the spermicidal action of Aureomycin, and particularly of its yellow pigment—administered either with a fungus culture or alone—a significant step forward may be realized in this approach to the problem of fertility control.

Summary and Conclusions

1. The fungus *Candida albicans* is the commonest pathogenic fungus found in the human vagina. However, a strain of *C. albicans* which is pathogenic to mice may occasionally be found in the human vagina and produce no symptoms.

2. Other species of Candida may produce symptoms as well as genera other than Candida. The mere presence of a positive fungus culture, however, does not indicate vaginitis.

3. The *C. krusei* has consistently been nonpathogenic.

4. It is impossible to maintain a strain of *C. krusei* in the normal human vagina, but if Aureomycin suppositories are given prior to inoculation and continued several days thereafter, cultures can be maintained at least until the next menstrual period.

5. A diabetic patient who consistently showed high blood sugar levels did maintain, through a number of menstrual cycles, a vaginal culture of *C. krusei* after a single inoculation. Two other diabetic patients with normal blood sugar values failed to maintain the culture, however.

6. Vaginal fungus cultures were not maintained in 5 pregnant women.

7. Only one strain of vaginal fungus seemed to have any effect upon sperm survival or motility in the cervical mucus. This was the *C. krusei.* Two patients who exhibited this organism spontaneously on repeated culture in several postcoital tests showed immotile sperm. Ten patients who maintained vaginal inoculations of *C. krusei* were examined for sperm survival, and all showed immotile sperm in the cervical mucus. All 10 of these patients had infertility problems. The same problems in maintaining the vaginal fungus were found in monkeys as were encountered in women. Owing to the presence of the postcoital vaginal plug in the macaque, examinations for live sperm in the presence of vaginal fluids were not satisfactory. However, one of 3 monkeys which had positive fungus cultures became pregnant.

8. From the observations obtained it appears that *C. krusei* may play a role in infertility in that the fungus may compete with sperm for some substance which helps maintain sperm motility in the cervical mucus. These observations are being further investigated in normal women.

Appreciation is expressed to Dr. L. J. Wickerham, Northern Regional Research Laboratory, Peoria, Illinois, who confirmed the identification of the strain of *C. krusei* used in the inoculation experiments, to Dr. A. B. Kupferberg of Ortho Research Foundation, who tested the *C. krusei* in vitro for spermicidal effects, and to Dr. J. N. Eastman of the Department of Obstetrics, Johns Hopkins Hospital, who made the facilities of the Obstetrical Outpatient Department available to us.

References

1. Castellani, A.: Philippine J. Sc., Section B, Med. Sc. **5**: 197, 1910. Quoted by Lodder, J., and Kreger-Van Rij, N. J. W.: The Yeasts, a Taxonomic Study, New York, 1952, Interscience Publishers, Inc.
2. Plass, E. D., Hesseltine, H. C., and Borts, I. H.: AM. J. OBST. & GYNEC. **21**: 320, 1931.
3. Lamb, J. H., and Lamb, M. L.: J. Infect. Dis. **56**: 8, 1935.
4 Martin, D. S., Jones, C. P., Yao, K. F., and Lee, L. E., Jr.: J. Bact. **34**: 99, 1937.
5. Schnoor, T. G.: Am. J. Trop. Med. **19**: 163, 1939.
6. Martin, D. S., and Jones, C. P.: J. Bact. **39**: 609, 1940.
7. Wood, John S.: Unpublished data.
8. Salvin, S. B.: J. Immunol. **69**: 89, 1952.
9. Buxton, C. L.: Personal communication.

OVARIAN SALVAGE IN ROUTINE ABDOMINAL HYSTERECTOMY

RICHARD H. GROGAN, M.D., AND CHRISTOPHER J. DUNCAN, M.D.,
BROOKLINE, MASS.

(From the Free Hospital For Women, Brookline, and the Department of Gynecology, Harvard Medical School)

AT THE present time there exists no unanimity of opinion as to the proper handling of ovaries at the time of routine abdominal hysterectomy performed for benign indications. This is due in a large part to an incomplete understanding of certain phases of ovarian physiology, particularly during the period of the so-called climacteric.

Which organ or organs assume the function of the ovary when and if the latter undergoes senescence? Is the life expectancy of the ovary shortened or prolonged in the absence of the uterus? Until the answers to these and similar questions are definitely known, any statement in this regard is mere opinion, and this is more often than not either based on personal experience or flavored with the so-called "sixth sense."

From this obvious confusion one is forced to adopt a conservative attitude concerning the disposition of ovaries under the terms of this discussion. Conservatism, so considered, should be predicated upon the maximum well-being of the patient, coupled with a minimum of operative risk from the surgical procedure itself.

In so far as the latter is concerned, all will agree that oophorectomy adds little or no appreciable operative hazard. The well-being of the patient, however, could conceivably be affected, depending upon the selective treatment of the adnexa (salvage or removal).

Again, conservatism is at best a relative term and, as such, is subject to change depending upon a better understanding of ovarian function, which, in turn, will be based upon proved facts rather than present-day conjecture. For example, fifteen years ago a subtotal hysterectomy was universally accepted as a sound conservative procedure. With the realization, however, that the cervical stump is prone to undergo malignant change in a small but definite percentage of cases, it is now agreed that such an operation is not conservative, and that a total hysterectomy is the procedure of choice.

Since no such proved statistics are available regarding the disposition of the ovaries at the time of hysterectomy, one must of necessity accept the present-day concepts in this regard until such time as there is definite objective evidence in support of or opposed to ovarian salvage.

In brief, the currently popular opinions may be classified in one of three groups: conservative, ultraconservative, and radical. The "conservatists" consider the age of the patient at the time of hysterectomy to be the most

important single factor. With this as a point of departure, followers of this school believe that over and beyond a certain age (45 to 50 years) all ovarian tissue should be removed with the uterus, whereas, under this selected age, at least one ovary should be salvaged, provided, of course, that it is grossly normal.

The "ultraconservatists" on the other hand, consider the age of the patient as being of no particular significance, and are equally convinced that no normal ovary should ever be removed. The "radicalists" are also of the opinion that age is not a factor, but, unlike the ultraconservatists, strongly urge the removal of all ovarian tissue at the time of hysterectomy with adequate substitution therapy (estrogenic) administered prior to the development of the surgical menopause.

As already inferred, the ideal approach to this problem would be from an objective point of view. Since this is not feasible at the moment for the reasons just outlined, we must of necessity resort to a subjective clinical study with its obvious limitations. This can be accomplished by a comparative analysis of a series of routine abdominal hysterectomies with salvage of the ovaries, as opposed to a similar series in which all ovarian tissue is removed, with special concern for the postoperative sequelae in so far as they reflect the well-being of the patient. The plan and purpose of this study were to make such an analysis.

Material

A total of 635 routine abdominal hysterectomies comprise this review, performed during the years 1941 to 1950, inclusive, by both the resident and visiting staffs at the Free Hospital For Women. Of the total number, one or both ovaries in 391 cases which were retained hereafter will be referred to as Series A. Two hundred and forty-four had bilateral oophorectomy at the time of the initial surgery, and will hereafter be referred to as Series B. Of the latter, 185 were from the ward service and 59 from private sources. The preponderance of cases in Series A is indicative of the present-day conservative feeling at this hospital. In recent years, however, total hysterectomy with bilateral oophorectomy has been performed more and more frequently by members of the Staff (Table I).

TABLE I. TOTAL HYSTERECTOMY WITH AND WITHOUT REMOVAL OF ADNEXA

	TOTAL NO. CASES	CASES FOLLOWED	PER CENT
Total hysterectomy without removal of adnexa	391	363	92.8
Total hysterectomy with removal of adnexa	244	214	87.7
Service	185	155	
Private	59	59	

Criteria for Selection of Cases

The total number, both series included, were consecutive cases in so far as they fulfilled certain definite criteria (Table II). Each patient was 39 years old or under. None had received hormonal treatment for at least six

months prior to hysterectomy. In addition, the preoperative histories were carefully reviewed, and those with either actual or suggestive menopausal symptoms were automatically excluded. In this way, the postoperative appearance of "neurovascular" symptoms consistent with the true menopause could be justifiably considered as sequelae of the surgical procedure.

TABLE II. CRITERIA FOR SELECTION OF CASES

CRITERIA	SERIES A	SERIES B
Age	39 years and under	39 years and under
Menstrual history	No menopause preoperatively	No menopause preoperatively
Adnexa	One or both ovaries "in situ"	Removed "in toto"
Preoperative Hormone	None	None (substitution therapy posthysterectomy)
Menopause	Typical "neurovascular syndrome"	Typical "neurovascular syndrome"
Follow-up	Minimum of 4 months	Minimum of 4 months

Furthermore, all were followed postoperatively for a minimum of four months and, in many instances, for as long as six to eight years (average 1.2 years). A careful pelvic examination was done at each postoperative visit, and all were questioned concerning the presence of pain, discharge, and menopausal symptoms. The follow-up percentage was 92.8 per cent in Series A, and 87.7 per cent in Series B.

Adequate substitution therapy in the form of estrogenic hormone was given to all patients of Series B. (In each instance, such therapy was initiated prior to the development of menopausal symptoms and, in each case, not later than the fifth postoperative day.) The estrogens were taken daily for a minimum of six months, then gradually discontinued, until at the end of one year the majority were able to do without medication. The necessity for such treatment was carefully explained to the patients, together with the untoward symptoms which would most probably ensue should they not follow the prescribed regime.

Indications for Surgery

Leiomyomas of the uterus, dysfunctional flow, and prolapse were the most frequently encountered indications on admission for abdominal hysterectomy (Table III). The relatively high incidence of prolapse is explainable by the fact that these cases were treated prior to 1945 when a combined procedure (plastic and laparotomy) was the hospital routine in this type of condition.

TABLE III. INDICATIONS FOR HYSTERECTOMY

	SERIES A	SERIES B
Leiomyomas of the uterus	106	55
Dysfunctional flow	64	30
Prolapse (cystocele and rectocele)	46	2
Pelvic inflammation	30	39
Carcinoma of cervix or endometrium (anaplasia)	26	19
Endometriosis	20	36
Adnexal pathology	18	14
Pelvic pain	15	7
	325	202
Other Indications	38	12
Total	363	214

Chronic pelvic inflammation also was a major etiological factor. This condition is seldom seen at the present time, with the use of the sulfonamides and antibiotics in the acute phase.

It is the opinion in this hospital that carcinoma in situ of the cervix is a legitimate indication for abdominal hysterectomy, since it is felt that this lesion is a definite stage of malignancy in the cervix.

Endometriosis unresponsive to conservative measures (medical or surgical) is also rapidly becoming a leading cause for such treatment.

The Analyses

As previously stated this review is primarily concerned with postoperative sequelae, in so far as they affect the well-being of the patient. These disturbances are enumerated in Table IV.

TABLE IV. SEQUELAE, BOTH SERIES

	SERIES A	SERIES B
Subsequent operation	19	—
Postoperative adnexal mass	20	—
Chronic cystic mastitis	20	3
Menopause	53	22
Vaginitis	9	4
Total	121 or 33.3%	29 or 13.5%

Subsequent surgery because of an adnexal mass productive of either severe pain, dyspareunia, or generalized pelvic discomfort was noted in 19 patients in Series A, as opposed to none in Series B. Two cases of this group were surgical emergencies with a preoperative diagnosis of acute intestinal obstruction. At laparotomy, a loop of small bowel was found adherent to the retained ovary in each case.

In addition, a definite adnexal mass (probably ovarian) was noted in another 20 patients of Series A. Though relatively asymptomatic and therefore not an indication for operation, their presence necessitated repeated follow-up examinations lest they become troublesome at a later date.

Of special interest was the complaint of definite breast discomfort in 20 patients in Series A, as opposed to only 3 in Series B. Careful review of the preoperative history and physical examination in each instance disclosed no such pre-existent disorder of the breasts. The 3 cases in Series B were believed to be an immediate effect of the substitutional therapy since complete relief was obtained by continuation of the estrogens.

Of the 20 cases in Series A, physical examination confirmed a definite basis for the complaint (chronic cystic mastitis) and all were treated specifically either by biopsy in suspicious cases or with hormones.

Although this is not statistically significant, yet, in view of the current trend toward surgical castration where carcinoma of the breast is concerned, the question of association must be considered.

Menopausal symptoms with a true "neurovascular" pattern as manifested by hot flushes, headaches, etc., and necessitating hormonal substitution therapy for relief were noted 53 times in Series A as opposed to 22 in Series B (corrected). Patients who demonstrated mere hyperexcitability readily controlled by barbiturates were not considered true examples of the menopause, and hence were not included.

Postoperative vaginitis (proved *Trichomonas vaginalis* in each instance) was observed in 9 cases of Series A, as opposed to 4 in Series B. Undoubtedly, hypoestrinism was the precipitating factor in these cases.

Thus, to recapitulate, 33.3 per cent of the patients in Series A as opposed to 13.5 per cent in Series B were found to have disturbing postoperative sequelae which, though not serious, certainly did not enhance their postoperative well-being.

From the point of view of this discussion the cases necessitating subsequent surgery, and those developing the true menopause were of primary concern and therefore merit detailed discussion.

In Table V are shown the histological reports of the initially salvaged ovaries which were subsequently removed. Of the total number, which represented 5.2 per cent of Series A, 8 showed simple follicle cysts, 7 had retention cysts secondary to perioophoritis, and the remaining 4 were found to have endometriosis not previously noted at the time of the initial operation.

TABLE V. SUBSEQUENT OOPHORECTOMY, SERIES A

PATHOLOGY	NUMBER
Cystic ovary	8
Chronic perioophoritis	7
Endometriosis	4
Total	19 or 5.2%

In no instance was carcinoma of the ovary found. This is in accord with the low incidence of this disease prior to the age of 40, and suggests that subsequent malignancy is not of paramount concern when the problem of ovarian salvage is considered.

As already mentioned, the true menopause was observed in 53 patients (14.6 per cent) with salvage of the ovaries and in 22 (corrected 10.3 per cent) with removal of all ovarian tissue, but with adequate hormonal substitution therapy. When bilateral oophorectomy was first proposed, 0.25 mg. of stilbestrol daily was thought to be sufficient. In many cases, however, this dosage proved to be inadequate, and menopausal symptoms were prone to appear. Thereupon, 0.5 mg. stilbestrol (and later estinyl, 0.05 mg.) starting on the fifth postoperative day was given, and better control assured. This represents a corrected incidence of 10.3 per cent.

It is thus evident that the true menopause was found to be less frequent in Series B with a known hormonal level (though admittedly substitutional) than in Series A where complete reliance for adequate control was placed upon a salvaged ovary or ovaries whose histological pattern was completely unknown, and whose life expectancy in the absence of the uterus was likewise enigmatic (Table VI).

TABLE VI. INCIDENCE OF MENOPAUSE

	CASES FOLLOWED	NO MENOPAUSE	MENOPAUSE	PER CENT MENOPAUSE
Series A (391 cases)	363	310	53	14.6
Series B (244 cases)	214	157	57	26.7
Series B after correction	214	192	22	10.3

Since the conservative school currently favors salvage and since its basic tenets revolve about the age of the individual together with the possibility of the postoperative menopause, this factor was a point of special interest.

Careful review disclosed that of the 53 patients in Series A who developed the menopause postoperatively the average age at the time of the hysterectomy was 33.8 years as opposed to 33.5 years where no menopause ensued. Again, in Series B, the average age of the patients with the postoperative menopause was 34.7 years at the time of hysterectomy as opposed to 34.6 years when no menopause followed (Table VII).

TABLE VII. AVERAGE AGE AT TIME OF HYSTERECTOMY

	CASES FOLLOWED	AGE AT MENOPAUSE	AGE NO MENOPAUSE
Series A (391 cases)	363	33.8 years	33.5 years
Series B (244 cases)	214	34.7 years	34.6 years

Thus, age, per se, does not appear to be a factor. Rather it seems that the fault rests in intrinsic ovarian change, which was either not discernible upon gross inspection at the time of laparotomy or developed after hysterectomy.

In support of this contention, further analysis of the patients with postoperative menopause in Series A disclosed the fact that 22, or 41.5 per cent, had dysfunctional flow of an anovulatory type preoperatively, which in itself was the primary indication for the abdominal hysterectomy (Table VIII).

Histological study of the initially removed ovaries, when available, disclosed either perioophoritis, multiple follicle cysts, or a senescent pattern. Hence, it is probable that the retained ovary was similarly involved, and yet, because this was not observed grossly at the time of the initial operation, it was left in situ (Table VIII).

TABLE VIII. RELATIONSHIP OF MENOPAUSAL SYNDROME TO PREOPERATIVE MENSTRUAL CYCLE

TOTAL	MENOPAUSE	REGULAR CATAMENIA	DYSFUNCTIONAL FLOW	PER CENT
Series A 363	53	31	22	41.5
Etiology of Dysfunctional Flow.—				
a. Perioophoritis		6	(previous surgery 3)	
b. Negative ovaries		6	(not removed 4)	
c. Multiple follicle cysts		6		
d. Senescent ovaries		4		
Total		22		

Summary

The salient objectives of conservative surgery are the well-being of the postoperative patient and the subjection of the individual to a minimum of danger from the technique of the operative procedure itself.

It is generally accepted that oophorectomy at the time of routine abdominal hysterectomy offers no operative hazard and probably facilitates the operative effort.

The definitive disposition of ovaries, however, could conceivably affect the well-being of the postoperative patient. This would best be reflected in a comparative analysis of the end results of a group of routine abdominal hysterectomies with ovarian salvage on the one hand as compared to a similar group with complete removal of all ovarian tissue.

The results of this study indicate that the terms of our definition of conservative surgery are best fulfilled, and the interests of the patient are best served by bilateral oophorectomy at the time of routine abdominal hysterectomy.

Conclusions

Six hundred and thirty-five routine abdominal hysterectomies have been reviewed. Of this number, one or both ovaries were salvaged in 391 cases; bilateral oophorectomy was done at the time of the initial procedure in 244 cases.

Thirty-three and three-tenths per cent of Series A presented disturbing postoperative problems as opposed to 13.5 per cent in Series B. In 5.2 per cent of Series A subsequent oophorectomy was necessary.

The postoperative surgical menopause was noted in 14.6 per cent of patients in Series A as opposed to a corrected incidence of 10.3 per cent in Series B.

The age of the patient at the time of hysterectomy is apparently not an important factor.

The high incidence of postoperative menopausal symptoms (41.5 per cent) with preoperative dysfunctional flow of the anovulatory type is noted.

DYSGERMINOMA OF THE OVARY*

Prognosis and Treatment

PAUL PEDOWITZ, M.D., F.A.C.S., BROOKLYN, N. Y., LAURENCE B. FELMUS, M.D., F.A.C.S., NEW ROCHELLE, N. Y., AND DAVID M. GRAYZEL, M.D., BROOKLYN, N. Y.

(From the Departments of Obstetrics, Gynecology, and Pathology, Jewish Hospital of Brooklyn, and the Department of Obstetrics and Gynecology, State University of New York at New York City, College of Medicine)

ALTHOUGH most pathologists are agreed that dysgerminoma of the ovary is a malignant neoplasm, there is considerable difference of opinion in regard to the degree of malignancy. Reported five-year survival rates vary from 12.5 to 66.7 per cent.[12, 19, 34, 38] In a recently published review of 427 cases of dysgerminoma, Mueller, Topkins, and Lapp[39] reported a five-year survival rate of 27.3 per cent, but another review[12] based on 83 cases, also published recently, reported a five-year survival of 63.8 per cent.

Since over 90 per cent of cases of dysgerminoma occur in young women and adolescents, several methods of treatment of these neoplasms, aimed at the preservation of fertility, have been widely adopted, especially by gynecologists who consider dysgerminoma as relatively benign. Others, however, believe that dysgerminoma possesses sufficient malignant potentiality to warrant removal of both adnexa and the uterus. We share this belief, which is based on a previous study of 17 cases of dysgerminoma, in which the five-year mortality was 70 per cent.[19] Only simple salpingo-oophorectomy had been performed on 12 of the patients: 9 were dead within five years.

While it is apparent that dysgerminoma, like other ovarian tumors of the dysontogenetic group, is less malignant than the more common forms of primary carcinoma of the ovary, it nevertheless has a higher potentiality for malignancy and recurrence than has heretofore been generally considered. In order to determine, if possible, the degree of malignancy, as well as the efficacy of various therapeutic measures employed for this disease, the literature was reviewed and all the cases of dysgerminoma reported since 1949 were studied (Table I).

This report is based on an analysis of 100 cases of dysgerminoma of the ovary which have appeared in the literature since the review of Mueller, Topkins, and Lapp, published in 1950. Two hitherto unreported cases from the Jewish Hospital of Brooklyn are added, making a total of 102 cases analyzed. Five-year follow-up information was available on 70 patients of whom 51 were dead, a mortality rate of 72.9 per cent. Only 19 of the 102 patients have survived five or more years, 27.1 per cent (Table II). Twenty of 32 patients with less than a five-year follow-up have been observed for less than one year, and the remaining 12 from one to five years.

*Presented at a meeting of the Brooklyn Gynecological Society on April 21, 1954.

TABLE I. CASES OF DYSGERMINOMA REPORTED SINCE 1949

AUTHOR	NO. CASES
Allan and Hertig[1]	2
Munnell and Taylor[2]	3
Tuominem and Auvinen[3]	5
Daiser[4]	1
Christensen[5]	1
Amorocho, Lichtenberger, and Becerra[6]	1
Jedberg[7]	2
Ber[8]	1
Veliath and Viswanathan[9]	5
Jacob[10]	2
Hain[11]	1
Mathieu and Plauchu[12]	11
Kostrubala, Thurston, and Chapin[13]	1
Chalmers[14]	2
Huyser[15]	1
Dhom[16]	1
Rotton and Trueblood[17]	1
Green[18]	2
Pedowitz and Grayzel[19]	17
Rosenthal[20]	1
Nenno[21]	1
Henderson[22]	7
Funck-Brentano[23]	1
Kirsch[24]	1
Kerr and Elkins[25]	2
Blondet[26]	1
Ravina, Seille, and Cheuilotte[27]	1
Ambre[28]	1
Ahnfelt[29]	4
Narat, Raider, and Carton[30]	1
Randall and Hall[31]	6
Anderman, Johnson, and Hosmer[32]	1
Galan and Valenzuela[33]	1
Looker, Callahan, and Barry[34]	5
Cowan and Feld[35]	2
Dunster and Bennett[36]	3
Falls, Czyz, and Ragins[37]	1
Authors	2
Total cases	102

TABLE II. FOLLOW-UP IN 102 CASES OF DYSGERMINOMA OF THE OVARY

TOTAL CASES	LESS THAN FIVE YEARS		FIVE OR MORE YEARS				
	LIVING			DEAD			SURVIVAL
	0-1 YEARS	1-5 YEARS	LIVING	0-1 YEARS	1-5 YEARS	TOTAL	%
102	20	12	19	37	14	70	27.1

Prognosis

Gross Appearance of the Tumor.—Survival is directly dependent upon the gross appearance of the neoplasm at operation. Perforation of the capsule, infiltration of adjacent pelvic organs, and metastasis (chiefly to omentum, lumboaortic nodes, liver, and more distant viscera) are all indicative of a poor outcome. In 30 cases the tumor had spread beyond the confines of the involved ovary, and only 3 of these patients lived 5 years, a 12 per cent survival. This is almost one-third the survival rate for encapsulated tumors, which was 35.6 per cent (Table III).

Bilateral ovarian involvement is also indicative of a poor prognosis. This occurred in 14 to 17 per cent of the cases reported in the literature, and sug-

gests either multiple primary foci or metastasis from the contralateral ovary. The opposite ovary appeared grossly normal in 47 patients with encapsulated tumors, so that only unilateral salpingo-oophorectomy was performed, only to be the site of metastasis or primary focus in 17 within two weeks to two years after operation. That the contralateral ovary was already involved at the time of operation is suggested by the fact that 14 cases appeared within the first six months.

TABLE III. PROGNOSIS BASED ON ENCAPSULATION OF TUMOR

	TOTAL CASES	FOLLOW-UP LESS THAN 5 YEARS	FIVE-YEAR FOLLOW-UP			
		LIVING	LIVING	DEAD	TOTAL	SURVIVAL %
Encapsulated	72	27	16	29	45	35.6
Nonencapsulated	30	5	3	22	25	12.0
Total	102	32	19	51	70	27.1

Dysgerminoma frequently is a rapidly growing tumor, and generally the larger the growth the graver is the prognosis. That small tumors may also be highly malignant is demonstrated by a case reported by Kostrubala and his co-workers,[13] wherein the sole evidence of malignancy was a metastatic nodule in the mandible. At autopsy this was disclosed to have had its origin in a dysgerminoma of the ovary measuring 5 cm. in diameter. Conversely, large tumors may be relatively benign; the largest at the Jewish Hospital measured 16 cm. in diameter, and was removed from a patient still alive after 18 years.

Microscopic Appearance of the Tumor.—The degree of malignancy of "pure" dysgerminoma cannot, at present, be gauged by its histologic appearance, although it has been attempted on the basis of marked cellularity, lack of stromatous structure, or number and type of mitoses.[40, 41]

Tumor cells within lymphatics or blood vessels of the ovary, mesovarium, or mesosalpinx indicate spread of the tumor, even though the capsule may appear to be intact. Extensive metastasis to the peritoneum, uterine ligaments, and contralateral ovary occurred in a patient six months after unilateral salpingo-oophorectomy for encapsulated dysgerminoma; the excised ovary showed tumor cells within the hilar blood vessels (Fig. 1).

Dysgerminoma in combination with teratoma or choriocarcinoma is particularly malignant. Death came within three months to two patients with dysgerminoma combined with choriocarcinoma*[19, 20, 45] (Fig. 2), and to one patient within six months when combined with teratoma.[14] Such combinations of dysgerminoma with teratoma and choriocarcinoma are probably more frequent than is generally suspected, and might be noted more often if more blocks from different representative areas of the tumor were studied. Santesson[38] noted combined neoplasms in 7 of 33 cases of dysgerminoma so studied. The occasionally positive pregnancy test obtained from patients with dysgerminoma is probably due to hormone secretion from a combined teratoma or choriocarcinoma.

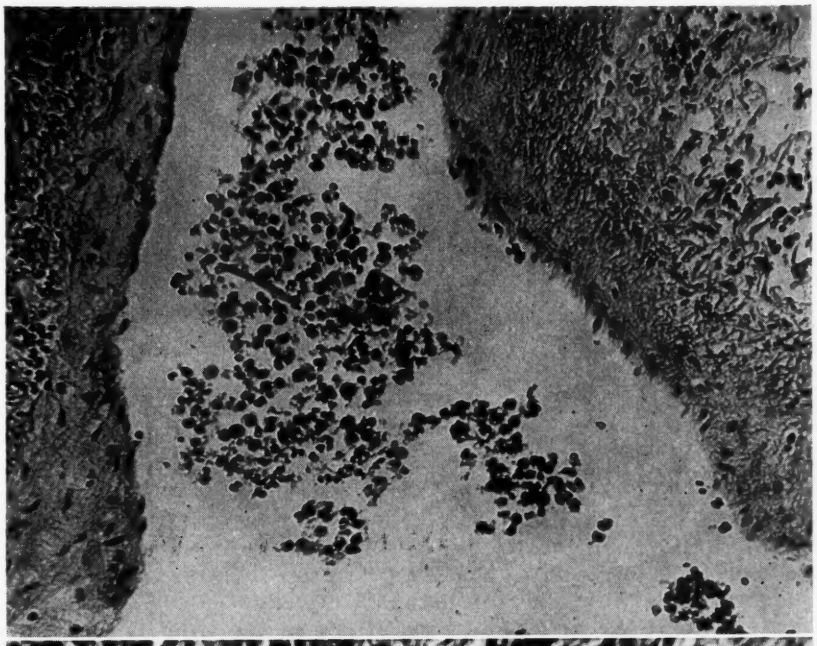
Age.—Girls under 15 years of age and women over 40 years had the lowest survival rates. There were 16 girls under 15 years in this series, and an equal number of women 40 years old and over. Two, or 18.2 per cent, of the younger age group survived five or more years; none of the older group survived five years, and 15 died within the first year after operation (Table IV). Dysgerminoma appeared to be least malignant in the 15 to 40 year age group, with a survival of 40 per cent.

*Refs. 19 and 45 refer to the same patient.

Ascites.—Clinically, hemorrhagic ascites was indicative of a poor outcome. No patients with hemorrhagic ascites survived five years (Table V).

Recurrence and Metastasis.—Recurrence of the tumor was associated with a 10 per cent five-year survival, compared to 86.5 per cent survival for patients without recurrence.

Fig. 1.



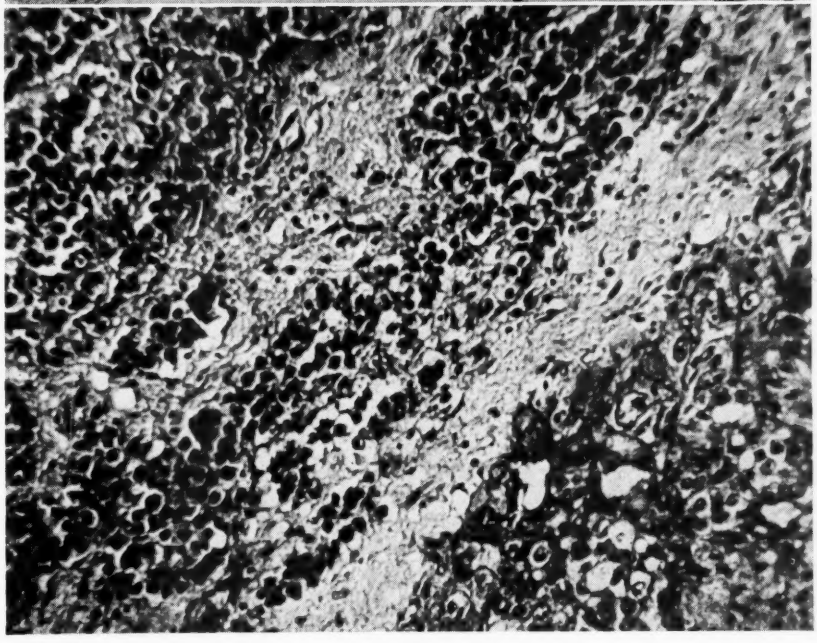


Fig. 2.

Fig. 1.—Dysgerminoma of the ovary. Tumor cells within hilar vessel. (Hematoxylin and eosin; ×440; reduced ⅙.)

Fig. 2.—Dysgerminoma combined with chorioçarcinoma. (Hematoxylin and eosin; ×100; reduced ⅙.)

TABLE IV. PROGNOSIS IN RELATION TO AGE

AGE OF PATIENT (YEARS)	NO. OF CASES	FOLLOW-UP LESS THAN 5 YEARS	FOLLOW-UP FIVE OR MORE YEARS				
				DEAD			SURVIVAL %
		LIVING	LIVING	0-1 YEARS	1-5 YEARS	TOTAL	
Under 9	6	3	0	2	1	3	0.0
10-14	10	2	2	6	0	6	25.0
15-19	19	9	4	3	3	6	40.0
20-29	33	14	7	9	3	12	36.8
30-39	9	3	3	1	2	3	50.0
40-49	4	0	0	3	1	4	0.0
50-59	6	1	0	5	0	5	0.0
60-69	4	0	0	4	0	4	0.0
Over 70	2	0	0	2	0	2	0.0
Unknown	9	0	3	2	4	6	33.3
Total	102	32	19*	37	14	51	27.1

*Four patients living more than 10 years.

TABLE V. PROGNOSIS IN RELATION TO TYPE OF ASCITES

	NO. CASES	FOLLOW-UP LESS THAN 5 YEARS	FOLLOW-UP FIVE OR MORE YEARS		
		LIVING	LIVING	DEAD	SURVIVAL %
Nonhemorrhagic	6	3	1	2	33.3
Hemorrhagic	8	2	0	6	0.0

The tumor recurred in 37 of 70 patients who had encapsulated dysgerminomas, and who survived the immediate postoperative period, a 52.9 per cent rate of recurrence. If a follow-up of one or more years had been available in all the cases of encapsulated neoplasms, the recurrence rate, in all likelihood, would be greater, but, unfortunately, the records were incomplete in many of the case histories.

Recurrences developed in 29 patients during the first year after operation, and more than half of these developed during the first six months. Recurrence, however, after the second year was so uncommon that a two-year survival without recurrence or metastasis appears to indicate a greatly increased chance of surviving at least five years (Table VI).

TABLE VI. PROGNOSIS IN RELATION TO TIME OF RECURRENCE IN 72 CASES OF ENCAPSULATED DYSGERMINOMA

INTERVAL (YEARS)	NO. CASES	FOLLOW-UP LESS THAN 5 YEARS	FOLLOW-UP FIVE OR MORE YEARS		
		LIVING	LIVING	DEAD	SURVIVAL %
Under 1	29	7	0	22	0.0
1-2	5	0	1	4	20.0
2-3	2	0	2	0	100.0
3-5	1	0	0	1	0 0
Total	37	7	3*	27	10.0
No Recurrence	35	20	13†	2‡	86.5
Grand Total	72	27	16	29	35.6

*One patient living more than 10 years.
†Three patients living more than 10 years.
‡Both patients died immediately postoperatively.

Clinical Picture

The signs and symptoms of dysgerminoma are those commonly associated with ovarian cancer in general, except for a more rapid development. Noticeably increasing enlargement of the abdomen, a palpable mass, and abdominal pain suggest a rapidly growing neoplasm of the ovary. Despite early diagnosis in many cases, tumors of the ovary were found to measure 10 cm., or more, at the time of operation. Large necrotic areas, frequently found within these tumors, are further evidence of very rapid growth, an indication of failure of the blood supply to keep pace with the increasing size. In part, this may also account for lower abdominal pain so often noted in these patients.

TABLE VII. CLINICAL FINDINGS IN 102 CASES OF DYSGERMINOMA

	NO. CASES	PER CENT
Abdominal enlargement	46	45.1
Abdominal mass	57	55.9
Pain	39	38.2
Distant metastasis	3	2.9
Acute abdominal crisis	15	14.7
No symptoms	5	4.9
Not stated	27	26.5

TABLE VIII. OPERATIVE FINDINGS IN 102 CASES OF DYSGERMINOMA

	NO. CASES	
Location of Tumor		
Right ovary	35	
Left ovary	32	
Both ovaries	6	
Not stated	29	
Total		102
Metastases	30	
Ascites		
Hemorrhagic	6	
Nonhemorrhagic	8	

TABLE IX. PROGNOSIS IN RELATION TO DURATION OF SYMPTOMS IN 102 CASES OF DYSGERMINOMA OF THE OVARY

DURATION OF SYMPTOMS	NO. CASES	FOLLOW-UP LESS THAN FIVE YEARS	FOLLOW-UP FIVE OR MORE YEARS		
		LIVING	LIVING	DEAD	SURVIVAL %
Less than 1 week	10	1	2	7	22.2
1 week-3 months	37	19	4	14	22.2
3 months-6 months	5	2	1	2	33.3
6 months-1 year	7	3	0	4	0.0
More than 1 year	5	4	1	0	100.0
Asymptomatic	5	1	0	4	0.0
Not stated	33	2	11	20	35.5
Total	102	32	19	51	27.1

Occasionally, the earliest symptoms of dysgerminoma of the ovary arise from metastasis outside the peritoneal cavity, as in the case reported by Kostrubala[13] previously described. In two other reported cases[14, 21] pleural effusion was the first evidence of ovarian disease. Torsion of the pedicle in 15 cases, with evidence of an acute abdominal crisis led to the diagnosis, and was

the earliest sign of ovarian tumor in 10 patients (although spread of the neoplasm had apparently already occurred in half of these). There were 14 patients with ascites (Tables VII and VIII).

The duration of symptoms bore no apparent relation to prognosis (Table IX).

Treatment

While there is general agreement that dysgerminoma is best treated surgically, there are marked differences of opinion in regard to the extent of the procedure. There is also some dispute about the necessity for postoperative radiation therapy in dealing with encapsulated tumors.

Preservation of the reproductive function in young women is highly desirable, so that the majority of gynecologists consider simple salpingo-oophorectomy sufficient treatment for women with encapsulated and freely mobile ovarian tumors.[31, 42] Hysterectomy and bilateral salpingo-oophorectomy are usually reserved for menopausal and postmenopausal women, and for those in whom the ovarian tumor is not encapsulated. Nevertheless, even in this latter group, extirpation of the uterus and both ovaries was carried out in only 5 of 16 patients beyond 40 years of age, and in only 7 of 30 with non-encapsulated growths (Tables X, XI).

TABLE X. END RESULTS OF SURGICAL TREATMENT IN 72 CASES OF ENCAPSULATED DYSGERMINOMA OF THE OVARY

OPERATION	NO. CASES	RECURRENCE	FOLLOW-UP LESS THAN FIVE YEARS	FOLLOW-UP FIVE OR MORE YEARS					
					DEAD				SURVIVAL %
			LIVING	LIVING	0-1 YEARS	1-2 YEARS	2-5 YEARS	TOTAL	
Salpingo-oophorectomy									
Unilateral	58	29	24	12	14	4	4	22	35.3
Bilateral	3	2	0	1	2	0	0	2	33.3
Hysterectomy	7	3	3	2	2	0	0	2	50.0
Not stated	4	3	0	1	3	0	0	3	25.0
Total	72	37	27	16	21	4	4	29	27.1

TABLE XI. END RESULTS OF SURGICAL TREATMENT IN 30 CASES OF NONENCAPSULATED DYSGERMINOMA OF THE OVARY

OPERATION	NO. CASES	FOLLOW-UP UNDER FIVE YEARS	FOLLOW-UP FIVE OR MORE YEARS					
				DEAD				SURVIVAL %
		LIVING	LIVING	0-1 YEARS	1-2 YEARS	2-5 YEARS	TOTAL	
Salpingo-oophorectomy	14	2	3	9	0	0	9	25.0
Hysterectomy	7	3	0	2	0	2	4	0.0
Exploratory laparotomy	4	0	0	4	0	0	4	0.0
Not stated	4	0	0	4	0	0	4	0.0
Autopsy	1	0	0	1	0	0	1	0.0
Total	30	5	3	20	0	2	22	12.0

In view of the high mortality and frequency of bilateral ovarian involvement, an increasing number of gynecologists believe that radical surgical

treatment should be performed in almost all cases of dysgerminoma of the ovary, even before extension of the growth beyond its capsule is evident.[19, 22, 38] This opinion is given support by evidence that 17, or 36.2 per cent, of 47 adequately followed cases of encapsulated dysgerminoma had involvement of the remaining ovary within a relatively short period of time after unilateral salpingo-oophorectomy—findings confirmed either at subsequent laparotomy or necropsy. If a later examination had been reported for the remaining 12 patients who died, the rate of contralateral involvement would have been over 50 per cent, in all probability. Recurrence of the dysgerminoma appeared in over half the cases within one month to a year after operation, an indication of probable involvement of the apparently normal contralateral ovary at the time of operation.

Spread of the malignancy to the lumbo-aortic nodes usually occurs early in the disease, so that inspection and palpation of those glands should form part of the surgical routine, and enlarged nodes should be biopsied. Involvement usually suggests a poor prognosis.

The value of postoperative x-ray therapy is uncertain, particularly where unilateral salpingo-oophorectomy had been done. Extensive irradiation, as for primary carcinoma of the ovary, obviously will nullify the advantages gained by the conservative operative procedure, particularly preservation of fertility. Another method of postoperative irradiation involves the shielding of the remaining ovary during treatment. In view of the 29.2 per cent bilateral involvement reported by Santesson[38] and the 36.2 per cent in the present study, however, to be effective, it appears that irradiation of the remaining ovary must be direct.

A third method of x-ray treatment involves the employment of only small-to-moderate amounts of radiation distributed over the entire pelvic region, so that ovarian function would not be impaired. While low-dosage irradiation is effective in destroying the well-known markedly radiosensitive dysgerminoma,[38] it would permit ovulation to continue to occur and production of detrimental mutations must be considered as a possibility.[44]

Only 42 per cent of the patients received postoperative x-ray therapy (Table XII), and no x-ray therapy was given to over 20 per cent of those patients who had metastasis or recurrence. The higher five-year survival rate and lowered mortality in the treated groups appear to indicate the value of x-ray therapy for both encapsulated and nonencapsulated tumors. The incidence of recurrence in encapsulated dysgerminoma was decreased by prophylactic irradiation, for recurrence developed in 37.5 per cent of the irradiated cases, as opposed to 62.2 per cent in the untreated group.

TABLE XII. INFLUENCE OF RADIATION THERAPY UPON DYSGERMINOMA (DATA AVAILABLE ON 95 CASES*)

TYPE OF TUMOR	NO. CASES	RECURRENCE	FOLLOW-UP LESS THAN FIVE YEARS	FOLLOW-UP FIVE OR MORE YEARS		
			LIVING	LIVING	DEAD	SURVIVAL %
Encapsulated						
Irradiated	24	9	8	7	9	43.7
Nonirradiated	45	28	19	8	18	30.8
Nonencapsulated						
Irradiated	18		5	3	10	23.1
Nonirradiated	8†		0	0	8	0.0

*No data available on 5 patients, 4 of whom died within five years. Two additional patients died immediately postoperatively.

†One patient received nitrogen mustard for generalized metastasis.

From Table XIII, the value of radiation therapy for recurrences may be noted in a higher five-year survival rate, compared to the almost invariably fatal outcome in the untreated cases.

TABLE XIII. INFLUENCE OF RADIATION THERAPY UPON RECURRENCE OF DYSGERMINOMA OF THE OVARY

	NO. CASES	FOLLOW-UP LESS THAN FIVE YEARS	FOLLOW-UP FIVE OR MORE YEARS		
		LIVING	LIVING	DEAD	SURVIVAL %
Irradiated	23	6	3	14	17.6
Nonirradiated	14	1	0	13	0.0

Comment

The growing impression that dysgerminoma is more malignant than has been heretofore realized is borne out by this study. Even should the 32 patients with less than a five-year follow-up survive for that time, the ultimate survival rate would rise only to 50 per cent. But since about one-third of these patients already have evidence of metastasis or recurrence, it is highly improbable that such a survival rate would be attained. Furthermore, dysgerminoma of the ovary is probably the most malignant of the dysontogenetic group of neoplasms, all of which are now generally considered to be malignant.

The fewer deaths from dysgerminoma in the 15 to 40 year age period, compared to the higher mortality in those below the age of 15 years and above 40 years (Table IV), have also been noted by Mathieu and Plauchu.[12] They explain this lowered mortality as a result of the hormonal levels associated with normal ovarian function during the reproductive period. This explanation does not account, however, for a comparably low death rate after ovarian function has been ablated in the middle-aged group. In the 15 to 40 year age group there were 46 patients, of whom 17 received postoperative x-ray therapy. Eight additional patients had both irradiation and a subsequent oophorectomy for recurrence of dysgerminoma within three years after removal of the primary tumor.

Conversely, preservation of ovarian function failed to influence the ultimately fatal outcome in 8 other patients, 7 of whom died within the first year following operation (Table XIV).

TABLE XIV. END RESULTS OF ATTEMPTS TO PRESERVE FERTILITY BY CONSERVATIVE SURGERY IN 64 CASES OF DYSGERMINOMA

PATIENT'S AGE (IN YEARS)	NO. OF CASES	DESTROYED BY					FERTILITY PRESERVED
		IMMEDIATE POSTOPERATIVE X-RAY	X-RAY, SURGERY, OR DEATH				
			IN LESS THAN 1 YEAR	IN 1-2 YEARS	IN 2-3 YEARS	IN 3-5 YEARS	
Less than 9	6	4	1	0	0	0	1
10-14	9	5	1	0	0	0	3
15-19	15	3	4	1	1	0	6
20-29	27	11	5	1	2	1	7
30-39	4	3	0	0	0	0	1
40+	3	3	0	0	0	0	0
Total	64	29	11	2	3	1	18*

*No postoperative follow-up information available in 7 cases.

The greater frequency of pelvic examinations usually performed in patients from 15 to 40 years of age probably accounts, in some measure, for the increased five-year survival rate for that group. Perhaps better results could be obtained if the other age groups were similarly examined more often, particularly when lower abdominal symptoms call attention to the pelvic region. Routine exploration of the pelvis during laparotomy for any cause should be standard procedure, particularly in young girls operated upon for nonexistent "acute appendicitis." In a previously reported case of dysgerminoma, a nonencapsulated tumor was discovered at a repeat laparotomy performed for persistence of abdominal symptoms in a 7-year-old child, seven months following removal of a "chronic appendix."[19]

Observed differences in the degree of malignancy of dysgerminoma in various age groups suggest the possibility that more than one type of tumor is present. The paradoxical behavior of encapsulated dysgerminomas, although treated similarly, may be explained on some such basis. For example, Dixon and Moore[43] have recently demonstrated that seminoma of the testicle, a tumor apparently identical with dysgerminoma of the ovary, is actually composed of many types of what had previously been considered independent neoplasms. Thus, a seminoma might be in "pure form," or in combination with embryonal carcinoma, teratoma, or choriocarcinoma. Of these various types, the least malignant is "pure" seminoma, whereas embryonal carcinoma, teratoma, and choriocarcinoma, either singly, or in combination with seminoma, are far more malignant. Although, as yet, embryonal carcinoma of the ovary, either alone or in combination, has not been reported, and combinations of dysgerminoma with teratoma and choriocarcinoma occur far less often than combinations of seminoma with these tumors do in the testis, nevertheless, it may be conjectured that the more malignant dysgerminomas probably do contain unsuspected components. It may be that examination of blocks from several representative areas of these ovarian neoplasms, with such possibilities in mind, eventually would reveal combined embryonal carcinoma, teratoma, or choriocarcinoma more frequently than has been hitherto noted.

TABLE XV. DURATION OF FERTILITY IN 35 PATIENTS TREATED CONSERVATIVELY WITHOUT IMMEDIATE POSTOPERATIVE IRRADIATION

INTERVAL SINCE OPERATION (YEARS)	NO. OF CASES	FERTILITY DESTROYED BY			FERTILITY PRESERVED	PREGNANCIES ACHIEVED
		DEATH	FURTHER SURGERY	LATER X-RAY		
Less than 1	19	7	4	0	8*	0
1-2	4	0	1	1	2	2
2-3	4	1	0	2	1	1
3-5	2	0	0	1	1	1
5-10	4	0	0	0	4	0
10-20	2	0	0	0	2	0
Total	35	8	5	4	18*	4†

*No postoperative follow-up information on 7 cases.

†Two patients received radiotherapy during the puerperium for recurrence of the tumor; one of these died from metastasis one year after delivery.

Since dysgerminoma is pre-eminently a disease of early life, preservation of childbearing is an important factor to consider in the treatment. Surgical procedures designed to accomplish this end, in most instances, have proved to be failures (Table XIV). In the childbearing-age group there were 81 patients, of whom 64 had unilateral salpingo-oophorectomy. However, any advantage that accrued from this conservatism was soon nullified in 46 of the latter patients, either by immediate postoperative irradiation (29 patients),

surgery for recurrence involving the remaining ovary, and irradiation, within a few months to four years (9 patients), or by death from the malignant process, itself, within three years (8 patients). Thus, only 18 of the 64 conservatively treated patients retained fertility for any reasonable length of time (Table XV), and in 7 of the latter no follow-up information was available. Pregnancy actually did occur in four patients, but in two of the latter ovarian function had to be destroyed by irradiation during the puerperium, because of recurrence of the tumor.

The diagnosis of dysgerminoma can rarely, if ever, be made by gross inspection of the tumor or from frozen section; microscopic examination of stained laboratory preparations is necessary. Biopsy of an apparently normal opposite ovary usually proves unsatisfactory, because a microscopic focus of tumor within the hilus of the ovary would more probably be missed than included in the tissue removed for examination. Reliance on such negative reports may give rise to a sense of false security and be tragically misleading, for, as previously noted, contralateral normal-appearing ovaries were probably involved by the malignant process in 14 patients at the time of the original laparotomy. All developed clinically detectable lesions within six months—3 within one month, after operation (Fig. 3).

Since preservation of fertility by removing only the involved ovary has proved futile in more than 70 per cent of the cases, from the point of view of prognosis it would be advantageous to remove a possibly unsuspected focus by removing the opposite ovary as well. In young women, this would mean reoperation after a definitive diagnosis of dysgerminoma, since the usual procedure for encapsulated neoplasms is unilateral extirpation. While reluctance to perform a second laparotomy is understandable, removal of the remaining adnexa and uterus appears justifiable on the basis of the high incidence of unsuspected bilateral involvement. Although comparative statistics of radical versus conservative surgical treatment are not available, total hysterectomy and bilateral salpingo-oophorectomy, followed by a course of deep x-ray therapy to the pelvis, appears to be the treatment of choice for these neoplasms. The end results could not be worse than those obtained with conservative therapy, and there is a strong possibility that a higher five-year salvage could be attained.

Santesson, at the Radiumhemmet in Stockholm, sought to obtain a midground by treating these patients with low-dosage irradiation distributed over the entire pelvic region and lower back, postoperatively, after removal of only the grossly involved ovary. In this method he hoped to preserve fertility and yet destroy the radiosensitive dysgerminoma foci. Of 15 patients so treated at the Radiumhemmet, only 2 developed permanent amenorrhea, and 3 actually became pregnant.

While it is true that permanent impairment of ovarian function may not occur with low-dosage irradiation, there is danger of production of detrimental mutations in highly significant numbers by radiation of the gonads, recently suggested by Muller.[44] It would be preferable to employ the same x-ray dosage for dysgerminoma as is used in the treatment of primary carcinoma of the ovary. Thus, since castration, in any case, is inevitable, the treatment of choice is total removal of the uterus and adnexa.

Refinement of technique may eventually make histologic grading possible, so that benign varieties of dysgerminoma may be distinguished from more malignant tumors. Fertility may then not be needlessly sacrificed in those women with relatively benign neoplasms.

Although frequent pelvic examinations, especially during the first postoperative year, possibly would uncover early involvement of the remaining

ovary (after unilateral salpingo-oophorectomy), such involvement may occur and remain undetected until the tumor has spread beyond the ovary. One patient returned to the clinic two weeks after routine pelvic check-up examination, because of the appearance of lower abdominal pain. Re-examination then showed an enlarged ovary, which at subsequent laparotomy was discovered to contain a metastatic nodule. In addition, the Fallopian tube, uterus, and peritoneum were also involved in the metastatic process (Fig. 3).

The prognostic factors previously discussed are clinically significant, but statistical analysis of the data shows a lack of positive findings. All observed differences are either of no significance statistically, or of borderline significance, and are related to the small number of patients available for five-year follow-up, although approximately one-fourth of all reported cases are included in the study. It is hoped that gynecologists will continue to report their experiences with dysgerminoma, so that it may soon be possible, if present trends continue, to make statements which may be statistically, as well as clinically, significant.

Fig. 3.—Dysgerminoma in contralateral ovary, discovered at autopsy. Ovary appeared grossly normal at operation three months before.

Summary and Conclusions

An analysis of 102 cases of dysgerminoma of the ovary, all reported since 1949, is presented. The survival rate of 70 cases with five-year follow-up was 27.1 per cent, and the mortality rate was 72.9 per cent.

Prognosis is influenced by nonencapsulation of the tumor, bilateral ovarian involvement, tumor cells within lymphatics or blood vessels of the ovary, combination of dysgerminoma with teratoma or choriocarcinoma, development of the tumor during prepuberal or postmenopausal years, hemorrhagic ascites, and recurrence of the neoplasm.

Dysgerminoma is more malignant than has been heretofore considered: 52.9 per cent of apparently encapsulated tumors recurred.

Contralateral involvement occurred in 17, or 36.4 per cent, of 47 conservatively operated upon patients with encapsulated dysgerminoma. Since 14 of these cases occurred within the first six months after operation, involvement was probably present at the time of laparotomy, either with a primary focus or a metastasis. The incidence of bilateral involvement, herein stated, is higher than most published statistics have previously indicated.

Follow-up studies of patients with unilateral salpingo-oophorectomy show loss of reproductive function in a majority, resulting from either subsequent irradiation of the gonad, reoperation with removal of the remaining ovary, or from death from the malignancy itself. Even when pregnancy was achieved, recurrence of the dysgerminoma necessitated pelvic irradiation during the puerperium in 2 of the patients, with consequent loss of fertility.

Conservative surgery, performed to preserve fertility, is almost always ultimately futile, and in view of the high degree of malignancy of dysgerminoma and the frequency of bilateral involvement, is not warranted. The preferred treatment appears to be bilateral salpingo-oophorectomy and total hysterectomy, to be followed by a postoperative course of deep x-ray therapy, regardless of the encapsulation or nonencapsulation of the tumor. Pelvic irradiation is indicated for recurrences.

Direct radiation to the remaining ovary, in cancerocidal dosage, may be employed in cases where reoperation is inadvisable. Low-dosage irradiation, while possibly preserving fertility, is inadvisable, in view of the probable genetic damage which may become manifest in future generations.

Varying degrees of malignancy of dysgerminoma of the ovary suggest that there may be different varieties of the tumor, analogous to seminoma of the testicle. It is postulated that more thorough histologic examination of issue blocks from several areas of the tumor may reveal a higher incidence of combined teratoma, choriocarcinoma, and embryonal carcinoma than has been reported, particularly in rapidly fatal cases.

We gratefully acknowledge the statistical analysis of our data by Dr. Schuyler G. Kohl.

Addendum.—Since the submission of this paper for publication, the following cases of dysgerminoma of the ovary were discovered, but were unavailable for analysis:

Blanchard, O.: Arch. Soc. cirujanos Chile **3**: 444, 1951. (2 cases.)
Mathevon, J.: Lyon chir. **46**: 759, 1951. (1 case.)
Picinelli, C.: Ann. obstet. e ginec. **72**: 595, 1950. (1 case.)
Lombard, P.: L'Afrique franç. chir. **2**: 113, 1951. (Not available.)
Zuckermann, C.: Rev. mex. cir., ginec. y cáncer **18**: 259, 1950. (1 case.)
Possolo Goulart (1950): Quoted by Munoz. (2 cases.)
Bianco, A., Disconzi, A., and Andrade, J.: An. brasil ginec. **18**: 35, 1953. (1 case.)
Munoz, A. V.: An. ginec. **1**: 93, 1953. (3 cases.)

Thus, a total of 540 definitely known cases of dysgerminoma of the ovary have been reported to date. The 427 cases reviewed by Mueller, Topkins, and Lapp,[39] 102 cases in the present series, and 11 cases of the addendum comprise this total. Since no information was available regarding Lombard's cases, they are not included in the figures.

References

1. Allan, M. S., and Hertig, A. T.: Am. J. Obst. & Gynec. **58**: 640, 1949.
2. Munnell, E. W., and Taylor, H. C., Jr.: Am. J. Obst. & Gynec. **58**: 943, 1949.

3. Tuominem, K., and Auvinen, E.: Ann. chir. et gynaec. Fenniae **38**: 496, 1949.
4. Daiser, K. W.: Strahlentherapie **79**: 243, 1949.
5. Christensen, A.: Ugesk. f. laeger **111**: 725, 1949.
6. Amorocho, J., Lichtenberger, E., and Becerra, A.: Rev. Fac. de Med., Bogota **17**: 610, 1949.
7. Jedberg, H.: Acta obst. et gynec. scandinav. **28**: 194, 1949.
8. Ber, A.: Acta med. scandinav. **133**: 411, 1949.
9. Veliath, G. D., and Viswanathan, G. S.: Indian J. Surg. **11**: 1, 1949.
10. Jacob, K. C.: Indian J. Surg. **11**: 210, 1949.
11. Hain, A. M.: J. Clin. Endocrinol. **9**: 1349, 1949.
12. Mathieu, J., and Plauchu, M.: Lyon chir. **45**: 76, 1950.
13. Kostrubala, J. G., Thurston, E. W., and Chapin, M. E.: Oral Surg. **3**: 1184, 1950.
14. Chalmers, J. A.: J. Obst. & Gynaec. Brit. Emp. **57**: 437, 1950.
15. Huyser, W. C.: J. Michigan M. Soc. **49**: 322, 1950.
16. Dhom, G. F.: Ztschr. f. Path. **61**: 430, 1950.
17. Rotton, G. N., and Trueblood, D. V.: West. J. Surg. **58**: 116, 1950.
18. Green, J. A. S.: Brit. M. J. **2**: 1098, 1950.
19. Pedowitz, P., and Grayzel, D. M.: AM. J. OBST. & GYNEC. **61**: 1243, 1951.
20. Rosenthal, A. H.: Personal communication.
21. Nenno, D. J.: AM. J. OBST. & GYNEC. **60**: 1390, 1950.
22. Henderson, D. N.: AM. J. OBST. & GYNEC. **62**: 816, 1951.
23. Funck-Brentano, F.: Paris méd. **41**: 6, 1951.
24. Kirsch, J.: Paris méd. **41**: 232, 1951.
25. Kerr, H. D., and Elkins, H. B.: Am. J. Roentgenol. **66**: 184, 1951.
26. Blondet, C.: Pathologica (Geneva) **43**: 64, 1951.
27. Ravina, A., Seille, G., and Cheuilotte, R.: Presse méd. **59**: 189, 1951.
28. Ambre, B. C.: Bull. Féd. Soc. gynéc. et obst. **3**: 656, 1951.
29. Ahnfelt, P.: Nord. med. **45**: 1006, 1951.
30. Narat, J. K., Raider, J. H., and Carton, A. K.: Surgery **30**: 859, 1951.
31. Randall, C. L., and Hall, D. W.: AM. J. OBST. & GYNEC. **63**: 497, 1952.
32. Anderman, L. B., Johnson, W. F., and Hosmer, F.: AM. J. OBST. & GYNEC. **63**: 464, 1952.
33. Galan, G., and Valenzuela, G.: Bol. Soc. chilena obst. y ginec. **17**: 129, 1952.
34. Looker, R. F., Callahan, W. P., and Barry, F. E.: Am. J. Surg. **85**: 4, 1953.
35. Cowan, I. I., and Feld, S. M.: AM. J. OBST. & GYNEC. **66**: 668, 1953.
36. Dunster, M., and Bennett, D.: J. Obst. & Gynaec. Brit. Emp. **60**: 402, 1953.
37. Falls, F. H., Czyz, S. I., and Ragins, A. B.: AM. J. OBST. & GYNEC. **66**: 897, 1953.
38. Santesson, L.: Acta radiol. **28**: 644, 1947.
39. Mueller, C. W., Topkins, P., and Lapp, W. A.: AM. J. OBST. & GYNEC. **60**: 153, 1950.
40. Foderl, V.: Arch. Gynäk. **165**: 392, 1938.
41. Seegar, G. E.: Arch. Surg. **37**: 697, 1938.
42. Novak, E.: Gynecologic and Obstetric Pathology, ed. 3, Philadelphia, 1952, W. B. Saunders Company, p. 400.
43. Dixon, F. J., and Moore, R. A.: Cancer **6**: 427, 1953.
44. Muller, H. J.: AM. J. OBST. & GYNEC. **67**: 467, 1954.
45. Neigus, I.: AM. J. OBST. & GYNEC. **69**: 838, 1955.
46. Weintraub, L., Rosenblatt, P., and Brandman, L.: AM. J. OBST. & GYNEC. **61**: 1167, 1951. (Report of 1 case included in Pedowitz and Grayzel series.[19])

9 PROSPECT PARK WEST (DR. PEDOWITZ)
524 NORTH AVE., NEW ROCHELLE (DR. FELMUS)
555 PROSPECT PLACE (DR. GRAYZEL)

THE FETUS CAN BLEED

Three Clinicopathological Pictures

BRUCE CHOWN, M.D., WINNIPEG, MANITOBA

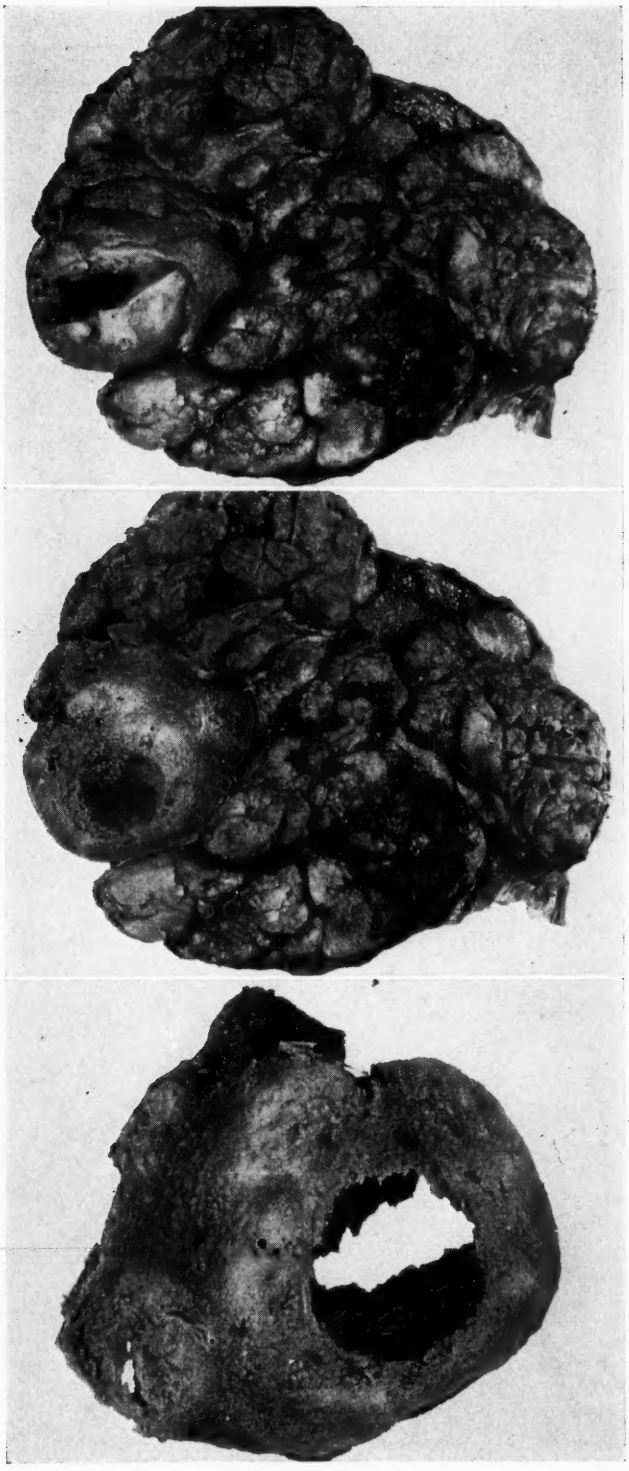
(From the Blood Group Reference and Research Laboratory, Children's Hospital, and the Department of Pediatrics, University of Manitoba)

WICKSTER and Christian[1] recently reviewed the recognized causes of posthemorrhagic anemia in the baby at birth. These are:

1. Abruptio placentae
2. Placenta previa with separation of the marginal area of attachment of the cord
3. Tearing, rupturing, or cutting of
   a. normal cord
   b. unsupported vessels
      i. in velamentous insertion of the cord
      ii. running to a succenturiate lobe
      iii. running between lobes of a bipartite or multipartite placenta
      iv. other abnormal vessels, including vasa previa
   c. vessels on the fetal surface of the placenta
   d. placenta at cesarean section when it is placed anteriorly
4. Occult fetal bleeding into the maternal circulation

The present report deals with two cases of proved and one of probable fetal bleeding. In the first case what is thought to be a new area of fetal bleeding, namely, in the substance of the placenta itself, is described. In the second, first proof of Wiener's[2] hypothesis of occult fetal bleeding into the maternal circulation is provided. In the third, a new concept is propounded, namely, that, in bleeding into the circulation of its mother, a fetus may cause her to have a transfusion reaction and may itself suffer as a result of that reaction.

CASE 1.—(Patient of Dr. J. Hartley Mather.) The first eight months of Mrs. MacM.'s second pregnancy passed without event. In the ninth month there was transient edema. At 8½ months she had abdominal pain and went to the hospital thinking this the beginning of labor, but the pain passed off and she went home the next day. At 5:00 A.M. the day before her expected date of delivery she was awakened with severe abdominal pain. It was not like labor pains. She walked the floor for two hours before calling Dr. Mather, who admitted her to the hospital at once. There was no vaginal bleeding. The abdominal pains soon merged with labor pains; the membranes ruptured spontaneously at 9:10 A.M. and the baby, a girl weighing 2,270 grams, was born at 9:27. Dr. Mather noted that there was more blood loss than usual in the third stage (the mother's hemoglobin next day was 12.5 Gm.), that the placenta felt boggy, and that one cotyledon was cystic. The baby was pale but her condition not alarming. One hour later the nurse recorded, "Color very pale, cry weak. Moves quite vigorously." Three hours after birth the baby's red cells were 1.69 million, hemoglobin 5.4 Gm. per 100 ml. of blood, with many nucleated red cells in the smear. The mother and baby were Group A, Rh positive, the baby was Coombs negative. Nonhemolytic anemia was diagnosed, a replacement transfusion given, and the baby progressed normally.



A.

B.

C.

Fig. 1.—Placenta from Case 1. *A*, The maternal surface after the cavity in the largest cotyledon had been opened by a cut. *B*, Horizontal section through placenta showing the base of the cavity. *C*, Enlargement of the cotyledon containing the cavity, looking toward the outer, maternal surface. In *B* and *C* note the pale zone around the cavity.

The baby had apparently lost much blood. The problem that faced us was how and when this loss had taken place. There was no rupture of the vessels of the cord or of the fetal surface of the placenta, but in the large cotyledon that Dr. Mather felt to be cystic there was a spheroidal cavity about 2.5 cm. in diameter, empty save for a few drops of blood. The placenta (Fig. 1) was fixed in Formalin and sent to Dr. A. T. Hertig, Professor of Pathology, Harvard Medical School, who provided the following report:

"*Gross Description.*—This fixed placenta weighs 485 grams and measures 15 by 8 cm. in width and varies from 2 to 5 cm. in thickness. A 1.5 cm. segment of umbilical cord, with normal vascular structure, is received separately. The membranes have been removed previously at the site of marginal attachment. The fetal surface has the normal glistening appearance, and there is a small amount of diffusely distributed subchorionic fibrin. The main placental vessels show no thrombosis grossly, but it is notable that they are relatively scant over the thickest part of the placenta. The marginal sinus is normal.

"The maternal surface shows irregular bulky cotyledons occupying almost two-thirds of the surface with the remaining portion occupied by an indented, wedge-shaped, thin, firm, whitish-yellow area grossly having the characteristic appearance of an old massive infarction. Exposed by a cut in the maternal surface over the largest cotyledon is a spherical, empty cavity 2.7 cm. in diameter, surrounded by a zone paler in color than the more distant villous tissue. No hemorrhage or infarction is present in this area grossly. One small bit of fibrin is present on the surface in one area. No definite bleeding point is seen.

"*Microscopic Examination and Interpretation.*—(7 H. and E. stain.) Sections from the cord show no lesion. The amnion is intact and normal. Sections taken from the large firm infarcted area show an old extensive infarction, primarily subchorionic in site. No cause for this infarct is apparent. Occasional associated focal areas of nonsuppurative degenerative changes are seen. Focal areas of nonspecific necrosis are seen in the small amount of decidua present over the maternal surface. No toxic effects are evident in decidual vessels, however. Sections from the area of the cavity show that the wall is made of well-preserved but strikingly bloodless villi, showing no degeneration whatever. There is no infarct, thrombosis, or inflammation present, as there is no evidence of old hemorrhage. The villi elsewhere in the hypertrophied area are not bloodless. In general the villi are relatively immature, as evidenced by only slight tendency to syncytial knotting. However, there are no definite stigmata of erythroblastosis. Immediately adjacent to the cavity occasional nucleated red blood cells from the fetal circulation can be demonstrated in the maternal intervillous spaces. It is impossible to identify any bleeding point. *Wm. B. Ober, M.D.*"

Dr. Hertig's comment was, "I have never seen a cavity formation just like this one before. In support of the hypothesis (that the fetus had bled into the placenta) we find the bloodless villi and intervillous nucleated RBC's (occasionally seen with traumatic lacerations), but beyond this it is impossible to go. Certainly this placenta does not exhibit definite toxic effects or erythroblastotic changes."

Our first reconstruction of events was as follows: Placental "infarction," cause unknown, took place quite some time before delivery. The process was gradual, with slow reduction in function of at least half of the placenta as it then existed. The nutrition of the remaining portion remained good. As fetal growth put greater demands upon this residual portion it hypertrophied, just as the placenta sometimes hypertrophies in the presence of severe erythroblastotic anemia.* The hypertrophic, young villi, bearing the pressures and

*It is to be noted that the placenta without cord or membranes weighed 485 grams, the baby 2,270 grams, a ratio of 1:4.7. The cotyledons of the infarcted portion were about the size one would expect for a baby of this size; the cotyledons of the remaining portion were abnormally large. The normal placental weight for such a baby is about 325 to 375 grams, so that the excess weight is 110 to 160 grams. If one were to assume that originally one-half the placenta become functionless by degrees, this would represent the loss of about this weight of functioning tissue. The excess weight of 160 grams at delivery could then be looked upon as hypertrophy to compensate for this loss.

strains of a full-term circulation, ruptured in the largest cotyledon, which, perhaps, was less well supported because it was marginal. With the onset of the increasing uterine contractions of early labor this cotyledon separated from its uterine attachment, the fetal blood from the ruptured villi poured out, the fetus suffered an acute exsanguinating hemorrhage, and the mother a concealed retroplacental, or more properly retromembranous, hemorrhage of fetal, and perhaps maternal, blood.

If this interpretation were correct, the figures of red blood count 1.69 million, hemoglobin 5.4 Gm. three hours after delivery would indicate that the hemorrhage amounted to about two-thirds of the fetus' blood. It seemed difficult to believe that this amount of blood could have been lost suddenly and the fetus survive. Could then bleeding have been going on for some time? The attack of abdominal pain that the mother had two weeks before delivery might indicate the time of first bleeding. If bleeding had in fact been going on for some time, some of the fetal blood might have entered the mother's circulation, and, since she had no antibodies against it, it would live a normal life span there. The mother would then have two populations of cells in circulation, a large population of her own native cells and a small population of recent, fetal, immigrant cells. We set out to see if this were the case.

The complete blood grouping of the family was:

Father: A_1; MsNs; P+; CDe.cde; kk; Fy(a+); Le(a-).
Mother: A_2; MSNs; P+; CDe.cDE; kk; Fy(a+); Le(a+).
Baby: A_1; NsNs; P+; CDe.CDe; kk; Fy(a+); Le(a-).

The only directly agglutinable factor in the baby's blood that was absent from the mother's, and that therefore would act as a tag for the baby's cells mixed with the mother's, was the factor A_1. We were unable to agglutinate any red cells in the mother's circulation with anti-A_1. This method of proof failed us.

Some persons of blood group A_2 have naturally occurring anti-A_1 in their serum. This antibody was not present in the mother's blood at the time of delivery or at 2 weeks or 3 months after delivery. Further, no antibody against the baby's cells was demonstrable in the mother's blood by the saline, albumin, and indirect Coombs methods 3 months after delivery. A second method of proof of the passage of fetal cells into the maternal circulation had failed us.

Finally we tried the biochemical approach. Dr. George Delory, Associate Professor of Biochemistry, measured the refractory hemoglobin in Mrs. MacM.'s blood on the day of delivery and three months after delivery by the method of White, Delory, and Israels.[3] By this method 5 to 10 per cent of the hemoglobin of the normal adult is "refractory." The measurements were 7 per cent in the first specimen, 8 per cent in the second. A third method of proof had failed us. It therefore seemed unlikely that the fetus had bled into the mother's circulation.

We reconsidered the situation, and finally thought the following the likely sequence, though one beyond proof: Bleeding began suddenly into the placenta a few hours before delivery; this sudden outflow quickly compressed the surrounding villi, so trapping the extravasated blood in a tense-walled cavity, larger than the cavity as we saw it, but not large enough to hold the 100 c.c. or more the fetus finally lost; both plasma volume readjustment and red cell replacement began; there was no more bleeding for some time; then during labor the cotyledon separated, the fetal blood poured out on the maternal surface of the placenta and, with the release of pressure, there was a final second hemorrhage from the area of injury through which by now no maternal blood was flowing. In this way one may account for the pericavital, pale,

bloodless zone (zone of hemorrhage and compression); for the few nucleated red cells in the contiguous maternal intervillous sinuses with no demonstrable fetal blood in the general circulation; for the readjustment of plasma volume and the large number of nucleated red cells present by three hours after birth; for the excessive blood loss in the third stage, noted by Dr. Mather.

In summary, then, this was a case of nonhemolytic anemia in the newborn in which the bleeding appeared to have taken place into and through the placenta, without positive evidence that any of the fetal blood got farther in the maternal circulation than the intervillous sinuses neighboring the area of hemorrhage.

CASE 2.—(Patient of Dr. A. M. Goodwin and Dr. Harry Medovy.) Mrs. W., Group B, Rh negative, without Rh antibodies, was delivered of a 2,840 gram girl at 5:00 A.M. Nov. 14, 1953, after a completely uneventful pregnancy and labor. There was no unusual bleeding. The placenta with cord and membranes weighed 765 grams; nothing abnormal was noted about it and it was discarded. At birth the baby's condition caused no alarm, though she was a little slow to breathe; the junior obstetric intern present at the delivery recorded "Apgar 6, becoming Apgar 9 in 10 min.," that is to say, the baby appeared normal to him 10 minutes after she was born. On admission to the nursery, however, she was seen to be pale, with rapid respirations. At 5 hours the red cells were 2.3 million, and the hemoglobin 7.8 Gm. per 100 ml. blood with many nucleated red cells. She was Group B, Rh positive, Coombs negative. Dr. Medovy made a diagnosis of nonhemolytic anemia and suggested that the case illustrated Wiener's[2] hypothesis of intrauterine fetal bleeding. A replacement transfusion was given and the baby progressed normally.

This case actually preceded Case 1 in time but is placed second because I wished first to set before the reader the anatomical and pathological appearance of a placenta into which a fetus apparently bled with resultant anemia. What I believe to have been the bleeding zone in that placenta lay in a hypertrophied, marginal cotyledon. In the present case the placenta, or some portion of it, was probably hypertrophied, for it weighed 765 grams against an average weight of 475 to 550 for the size of the baby. There may well have been one or more points of rupture as in Case 1. That we can never know, but what this case did allow us to prove was that the baby had bled in quantity, and probably over a period of several weeks, into the mother's circulation. Proof was possible because of the fortunate, for us,* blood-group differences between mother and baby. The blood grouping of the family was:

Father:	O;	MS;	P+;	$C^wDe.CDe$;	kk;	Lu(a-); Fy(a+); Le(a-).
Mother:	B;	MNS;	P+;	cde.cde;	kk;	Lu(a-); Fy(a+); Le(a-).
Baby:	B;	MNS;	P+;	$C^wDe.cde$;	kk;	Lu(a-); Fy(a+); Le(a-).

The baby had the readily agglutinable agglutinogens C^w and D; the mother did not. Careful agglutination of the mother's blood with anti-C^w and with anti-D showed that some cells in her circulation carried these agglutinogens. By comparing the size of agglutinates in her blood with the size of agglutinates in artificial mixtures of Rh-positive and Rh-negative blood we estimated that 5 to 10 per cent of the mother's red cells were Rh positive, i.e., were red cells of the fetus. In confirmation the mother's blood absorbed anti-D (Rh) antibody to about the same degree as did a 5 to 10 per cent mixture of Rh-positive cells in Rh-negative cells. And, finally, Dr. Delory found Mrs. W.'s blood to contain 11 per cent of refractory hemoglobin on the day of delivery and only 5 per cent forty-eight days after delivery. We estimated that 5 per cent of maternal blood would be about 90 c.c. of red cells, or 160 c.c. of whole blood, which amount the fetus would have had to lose from a circulation of about

*Since this report was written, Mrs. W. has given birth to a second Rh-positive baby; it had moderate hemolytic disease and did well after a single replacement transfusion. Mrs. W.'s antibody titer was 16 throughout pregnancy.

210 c.c. A sudden loss of such an amount could not have been borne; the loss must have been a slow one over some weeks. In confirmation of this the mother had anti-Rh antibodies demonstrable on the twentieth day post partum: experimentally it takes 3 to 4 months from the first injection of Rh-positive cells before antibodies are demonstrable in an Rh-negative person. These observations have been reported in somewhat greater detail elsewhere.[4]

In thinking about this second case we wondered what would have happened had bleeding of this degree occurred into the blood stream of a woman who had antibodies against the fetal cells. It seemed to us that the mother should have a transfusion reaction of some kind, anything from a fleeting chill to hemoglobinuria, oliguria, jaundice. We gave little thought to what might happen to the baby under these circumstances, although, quite apart from the question of antibodies, it seemed likely that a fetus might well die in utero by bleeding too much. It was not long before we observed a case that seemed at once to add strength to our guess about the possible maternal reaction and to raise new questions.

CASE 3.—(Patient of Dr. Ida Armstrong.) Mrs. H. was Rh negative with an anti-D antibody titer of 16 in albumin; her previous baby had been stillborn near term with all the pathological signs of erythroblastosis. At 12:00 noon on Saturday, Feb. 6, 1954, Dr. Armstrong, on my advice, ruptured the membranes of Mrs. H., three weeks before term. Saturday and Sunday passed without event. Mrs. H. slept from 10:00 P.M. Sunday to 6:00 A.M. Monday, at which time she said she was cold. The fetal heart sounds were good. There were mild uterine contractions at three-minute intervals. She voided. By 8:00 A.M. she was flushed; the temperature was 98.4° F. The fetal heart sounds could no longer be heard. Contractions were mild to moderate at three-minute intervals. By 9:00 A.M. she was shivering violently and her temperature was 103.8° F.; pulse 132; she became nauseated and vomited. By 10:00 A.M. contractions were at two-minute intervals. The fetal heart sounds could not be heard. She was given 100 mg. Demerol. At 11:00 A.M. she was catheterized and a specimen of blood drawn. At 11:11 A.M. she gave birth to a boy weighing 2,550 grams. To our surprise he was alive. He breathed spontaneously, but lay limp and pale, as though in shock. Twenty minutes later he began to bleed from the nose, a slow, bright red trickle. This increased. At one hour he was given 50 c.c. of fresh heparinized blood. The bleeding continued. At two hours, twenty minutes he died. By this time the mother's temperature was normal and remained so.

Laboratory Findings.—The cord hemoglobin was 11.6 Gm. per 100 ml. blood; bilirubin 3.6 mg. per cent. In blood drawn just before death the fibrinogen was 160 mg. per cent; the one-stage prothrombin time 16 per cent of adult normal. The mother's blood drawn at 11:00 A.M. contained no demonstrable fetal cells; the bilirubin was 0.5 mg. per cent; there was no free hemoglobin. The urine at that time contained no casts. Maternal antibody:

	ALBUMIN							SALINE
	1	2	4	8	16	32	64	
Dec. 9	S	S	++++	++	$\bar{\pm}$			0
Dec. 30	S	S	++++	$++^{+}$	$\bar{\pm}$			0
Feb. 4	S	S	S-	$++^{+}$	$\bar{\pm}$			1
Feb. 8	S	S	S-	$+++^{+}$	$\bar{\pm}$			1
Feb. 11	S	S	S-	++++	+	$\bar{+}$		1
Feb. 20	S	S	S	++++	$+++^{+}$	$+^{+}$	$\bar{+}$	1

S = a single solid agglutinate; S- = almost completely solid agglutinate; the gradations are then ++++, $+++^{+}$, +++, $++^{+}$, ++, $+^{+}$, +, $\bar{+}$, $\bar{\pm}$, the last two being negative to the naked eye but positive microscopically.

An autopsy on the baby was done 20 hours after death. The larynx and trachea contained a small amount of hemorrhagic fluid; the lungs had a dark red hemorrhagic appearance. There was about 5 c.c. of blood in the posterior cranial fossa and 20 in the stomach, with petechiae in the mucosa of the latter. Microscopically, while the alveoli of the lungs were well expanded there was little air in them, but rather various proportions of blood and edema fluid, with more fluid than red cells. Scattered through them were many gram-positive bacilli. Polymorphonuclear cells and epithelial squames were rare. There was marked edema of the septal tissues. *Cl. welchii* was grown from both lungs, and a staphylococcus from the right. The other findings were typical of erythroblastosis.

The placenta (Fig. 2) was submitted to Dr. Hertig, who again provided a detailed report, as follows:

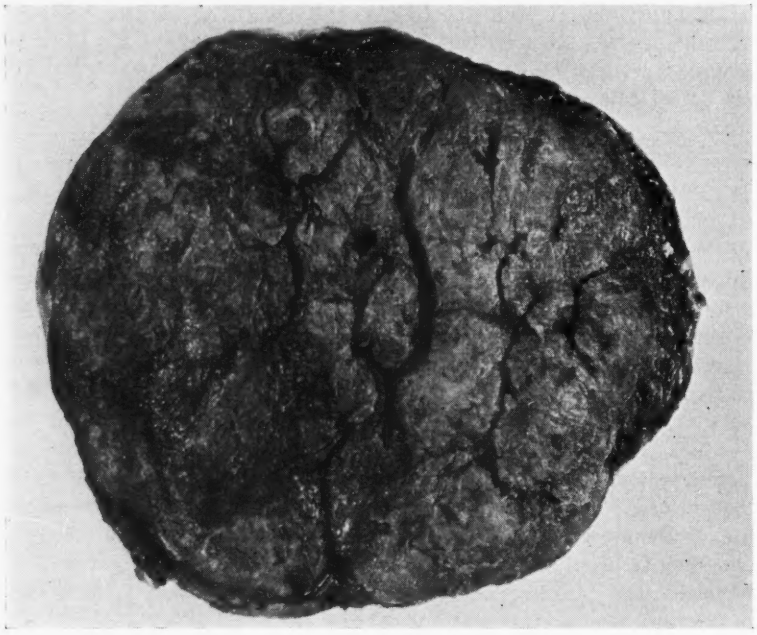


Fig. 2A.—Placenta from Case 3. The maternal surface.

"*Gross Description.*—This placenta weighs 420 grams and measures 15 by 16 cm. in width. The thickness is uniformly 2.5 cm. A 1 cm. segment of umbilical cord is attached eccentrically and a 22 cm. segment of cord is received separately. One large artery instead of 2, and one large vein are present throughout the cord. No thrombosis is evident. The membranes have been sheared off at their marginal attachment. The fetal surface presents a normal glistening appearance, and the usual moderate amount of patchy subchorionic fibrin is present. The maternal surface shows only slight fissuring. It is of dark color as is the cut surface, and no infarct, intervillous thrombosis or hydropic degeneration is apparent. The consistency is uniformly moderately firm. Near the center of the maternal surface is a tiny laceration 0.7 by 0.3 cm. by 1.2 cm. in depth, which is not associated with any focal degenerative change, but the surrounding villous tissue shows focal hemorrhagic discoloration. *D. W. Thompson, M.D.*

"*Microscopic Examination and Interpretation.*—(4 H. and E. stain.) The cord shows no lesion of the anomalously formed vessels. There is no chorioamnionitis or deciduitis. Though most of the placenta shows mature villi with areas of calcification and extensive intervillous fibrin associated with aging, there are focal areas of relative immaturity of villi. There are, however, insufficient changes in the nature of immaturity, cellularity, and increased vascularity of villi to substantiate a diagnosis of erythroblastosis. The fetal circulation, however, contains abnormal numbers of nucleated RBC's for this stage of

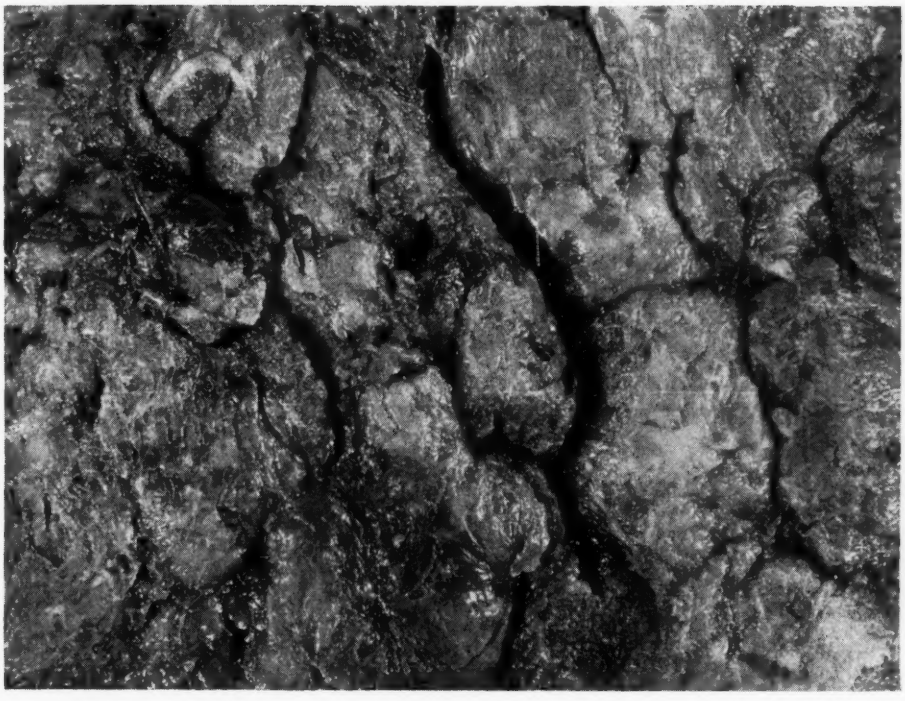


Fig 2*B*.—Placenta from Case 3. Enlargement of central area of maternal surface to show the defect.

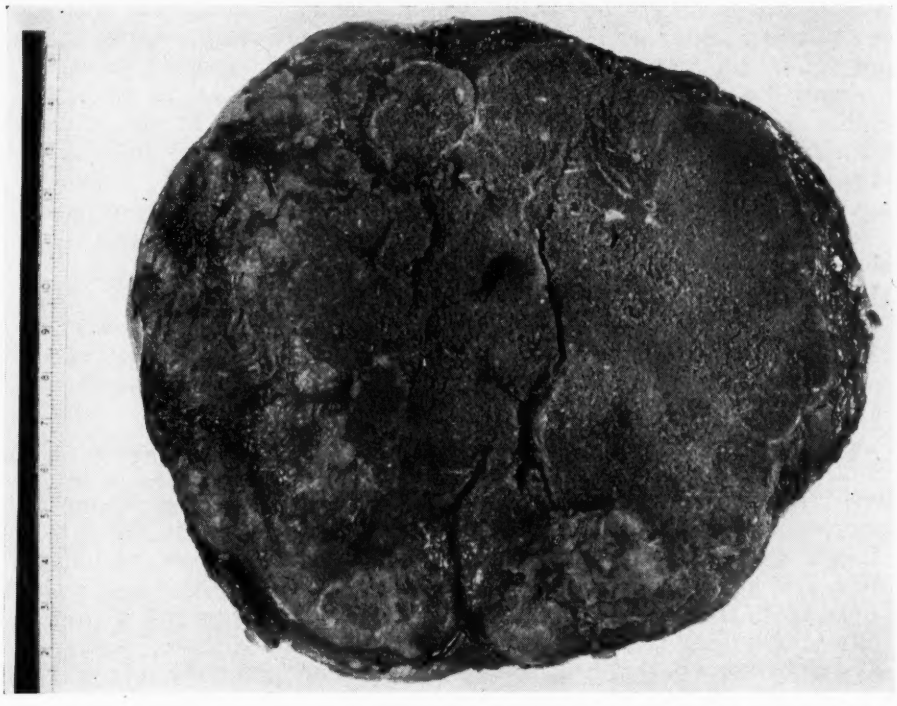


Fig. 2*C*.—Placenta from Case 3. Horizontal sections at 11 mm. from the surface showing the hemorrhagic base of the defect. Note that the defect lies in the center of a cotyledon and not at its margin.

development. In the area of laceration no inflammation is apparent, but there is hemorrhage present, some of which is made up of nucleated red blood cells. Again whether or not this is traumatic is difficult to say. There is no decidua in this area so it is difficult to assess completely the maternal aspect in this focal area. There is no evidence elsewhere of retroplacental hemorrhage and there is no marginal sinus thrombosis. *Wm. B. Ober, M.D.*"

From what has gone before, the reader will not be surprised at my primary deduction—that shortly before 6:00 A.M. on Monday the fetus bled into its placenta, the blood passed into the mother's circulation and produced in her a transfusion reaction. The evidence is the chill, the placenta, the maternal antibody curve, the shocked, and perhaps the hemorrhagic, state of the baby at birth.

The mother received antibiotics prophylactically from the time of rupture of the membranes. Up to the onset of the chill she felt well: her temperature was normal again by the time the baby was born and remained so. It is difficult to imagine that the chill was due to infection, although the bacteria in the baby's lungs at autopsy, even in the absence of inflammatory response, could support the interpretation that the chill was so caused. Failure to obtain evidence of hemolysis in examination of the blood and urine of the mother five hours after the symptoms began does not prove that hemolysis had not taken place: the actual amount of bleeding may have been small, and it will be seen from the record that she voided at 6:00 A.M., i.e., shortly after the symptoms of the chill began. The products of hemolysis might have been cleared by that time.

The placenta has already been described and illustrated. It was delivered spontaneously without pressure or traction, for our attention was focused upon the baby, who we thought was dead in utero but was born alive. I took the placenta within a minute or two of its expulsion and laid it flat on the table, maternal side up. There before me was a lesion which agreed with what I had guessed had happened: that the baby had bled into the mother and that she had suffered a transfusion reaction. Blood welled up slowly in the rent, which emptied as I picked the placenta up gently, only to fill again when it was again laid on the table. Obviously there was little object in grouping blood one might so recover. I admit my prejudice, but the lesion *is* compatible with the hypothesis. Furthermore, the lesion is close to the center of the maternal surface of the placenta in contrast to the peripheral position of the lesion in Case 1; extravasated blood at this point could not so readily escape between placenta and uterus.

The mother's antibody curve is compatible with the hypothesis that fetal blood reached the maternal circulation on February 8 and stimulated a moderate increase in the titer. Such a postnatal rise is, however, not uncommon in the absence of any recognized symptoms in the mother; we have often seen it.

The baby was much more "knocked out" at birth than one would expect an erythroblastotic baby to be with a hemoglobin of 11.6 Gm. This is not a very low level; I have seen many babies with a lower who scarcely appeared ill and were easily treated. Something unusual had happened to the baby. Nor have I ever seen bleeding like this before in erythroblastosis; bleeding from the lungs, yes, but usually on the second or third day, and then not more than a little red froth from the nose and mouth, though the lungs may contain much blood; but here was bleeding visible within twenty minutes, perhaps three ounces lost before the baby died two hours later. Our data on the blood-clotting factors of the baby are unfortunately incomplete. The specimens were taken as we were about to start a replacement transfusion and one was contaminated with heparin. The questions, it appears to me, are: Was the

baby's hemorrhagic state related to the mother's chill? If the mother's chill was indeed a mild transfusion reaction, did she produce and transmit to the baby a thrombolytic or heparin-like substance that produced the bleeding tendency in the baby but was inadequate to produce hemorrhage in her? (Transfusion reactions at times may result in uncontrollable hemorrhage.[5]) Was the baby suffering from hemorrhagic shock without blood dilution? We cannot answer these questions, but in asking them others may find the answer. The only comparable case I have been able to find was that reported by Rice.[6] No details of the delivery are available.

The evidence then cannot be considered decisive: we cannot *prove* that the baby bled, that the mother reacted, and that the baby's shocked and hemorrhagic state resulted. We think the hypothesis reasonable.

Comment

The evidence is unequivocal that a large volume of blood may pass from fetus to mother (Case 2). The evidence is strong that a large volume of blood may be lost by the fetus into and through its placenta (Case 1). The evidence is suggestive that the fetal blood may enter the circulation of a woman sensitized to that blood and thereby cause a transfusion reaction in her, possibly with a bad effect upon the fetus (Case 3).

How often fetal blood enters the maternal circulation we do not know, and we will not know until we have direct proof as in Case 2. Such proof we are seeking. In the meantime there seems little profit to review or enter into the controversy on this subject deriving from pathological observations.

I am not an obstetrician (indeed I managed to scrape through medical school without attending a single confinement). But these chance observations, and the reading they have provoked me to, have made me wonder about some obstetrical problems. One is, what part of the blood in a retroplacental hemorrhage is fetal, and may part of the maternal reactions in this condition be a true transfusion reaction to incompatible fetal cells? Another is what symptoms may a woman with antibodies against the red cells of her fetus develop if the fetus bleeds into her circulation? Experimentally, the rapid intravenous injection of as little as 2 c.c. of incompatible blood may, in some people, cause headache, joint pains, backache, symptoms suggestive of the onset of influenza. With a little more blood there may be chills and fever. Presumably transfusion of fetal blood can produce these symptoms in a pregnant woman, as suggested in Case 3. But is fetal transfusion of a mother ever large enough to produce jaundice, or hemoglobinuria, or oliguria in her? I hope an obstetrician somewhere will answer this question, I am intrigued by it.*

*Proof would depend upon (a) demonstration of antibodies in the mother's blood against the fetal cells; (b) probably an unusually low titer of such antibodies at the onset of symptoms because of absorption of part of the antibodies by the transfused fetal cells; (c) a subsequent rise in titer and pcssibly the development of one or more additional antibodies against other antigens in the fetal cells; (d) perhaps demonstration of the hemoglobin in the mother's plasma or urine being "refractory," i.e., fetal, although I do not know if this is possible. If the clots in the large vessels on the fetal surface of the placenta are dissected out and shaken up in saline, a cell suspension suitable for complete blood grouping can be obtained even when the fetus has been dead for several days; the blood in the fetal heart and in the vessels of the cord hemolyzes rather quickly after death and is rarely suitable for this purpose.

Summary

Three cases are reported, two of nonhemolytic anemia of the newborn with recovery, and one of fatal hemorrhage in an erythroblastotic baby. In the first case the mother lost more blood in the third stage of labor than usual, and a gross defect was found in the placenta. It is suggested that the fetus bled into and through its placenta, producing anemia in itself and a concealed retroplacental hemorrhage in the mother. In the second case it was proved that the baby had bled symptomlessly into the mother's circulation, and that the bleeding had been going on probably for several weeks before delivery. In the third case the mother had a chill and fever a few hours before delivery: there was a small defect in the placenta; the baby began to bleed a few minutes after birth. It is suggested that the mother's chill and fever were reactions to transfusions of the incompatible blood of the baby, and that the bleeding in the baby in some way resulted from this reaction.

This report was possible only through the wholehearted cooperation of Drs. Mather, Goodwin, Medovy, and Armstrong. It was, in fact, Dr. Medovy's suggestion that the second case illustrated Wiener's hypothesis which led to the whole investigation. The two successful replacement transfusions were done by Dr. J. M. Bowman, the detailed blood grouping by my associate Marion Lewis. I am most grateful to Dr. Hertig for his reports on the two placentas.

References

1. Wickster, G. Z., and Christian, J. R.: Pediat. Clin. North America **1**: 555, 1954.
2. Wiener, A. S.: Am. J. Obst. & Gynec. **56**: 717, 1948.
3. White, F. D., Delory, G. E., and Israels, L. G.: Canad. J. Research, Sect. E, **28**: 231, 1950.
4. Chown, B.: Lancet **1**: 1213, 1954.
5. Wiener, A. S., and Peters, H. R.: Ann. Int. Med. **13**: 2306, 1940.
6. Rice, W. G.: J. Pediat. **42**: 231, 1953.

MEGALOBLASTIC ANEMIA OF PREGNANCY AND THE PUERPERIUM*†

LOUIS LOWENSTEIN, M.D., CHARLES PICK, M.D., AND NEWELL PHILPOTT, M.D.,
MONTREAL, QUEBEC

WITH THE TECHNICAL ASSISTANCE OF
MADELEINE LALONDE

(From the Haematology Service of the Department of Medicine and the Department of Obstetrics and Gynaecology of the Royal Victoria Hospital, McGill Medical School)

THIS paper records observations on eighteen patients with megaloblastic anemia associated with pregnancy, the puerperium, or both, who attended the Royal Victoria Montreal Maternity Hospital during the three years 1949-1952. One patient was studied during a previous pregnancy in 1948. Routine antepartum hematological studies were used to detect anemia in these patients. Although the same screening has continued during the past one and one-half years, no patient with this form of megaloblastic anemia has been found during the latter period, due probably to reasons to be discussed later.

In most patients the diagnosis of megaloblastic anemia associated with pregnancy and the puerperium can be established only by bone marrow examination. Other megaloblastic anemias must be excluded. Many believe that this anemia is different in temperate climates from that found in the tropics. This is not a homogenous group of anemias. Although some of our patients suffered from intercurrent infection, the history of inadequate diet in most cases, the hematological findings, and the response to therapy (including vitamin B_{12}) indicate that nutritional deficiency caused the anemia in the majority of our patients. Bone marrow findings in these patients, as compared with those of normal pregnancy and nonmegaloblastic anemias associated with pregnancy suggest that all degrees of megaloblastic anemia may occur during pregnancy and the puerperium.

Methods

Initial hematological studies are performed by methods previously described[1, 2] at the time of the patient's first visit to the obstetrical clinic or, in the case of private patients, within a few days after the first visit to the obstetrician. A second study is made in the eighth month of pregnancy. Patients who are suspected of having pathological anemia are referred for complete study. The sternum was the usual site for bone marrow aspiration and 0.1 to 0.2 ml. was withdrawn. Supravital preparations were made using Janus green and neutral red. Cover slip preparations and slide preparations of marrow particles were stained with Jenner-Giemsa. A minimum differential count of 500 cells, often prolonged to 1,000 cells, was performed by one

*Presented at the Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, June 10, 1954.

†Supported by a Federal-Provincial grant in aid of Research by the Department of Health and National Welfare of Canada.

of us (L. L.). In the bone marrow differential counts, nucleated red cells were classified into three groups: megaloblasts, intermediate megaloblasts, and normoblasts. Each of these groups was divided into: pro-forms, basophilic, polychromatophilic, and orthochromatophilic or pyknotic forms. In the charts the pro-forms and basophilic blasts are grouped together as "early stages of maturation" and the polychromatophilic and orthochromatophilic blasts as "late stages of maturation." In some cases the early red cell was called a proerythroblast when it had not differentiated sufficiently to permit classification as a promegaloblast, pronormoblast, or intermediate promegaloblast. The percentage of different groups given in the case histories or charts is the percentage of the total nucleated red cells counted. In calculating the erythrogenic-leukogenic ratio, ordinary stab and polymorphonuclear granulocytes were not counted in order to avoid the factor of blood dilution. The macrogranulocyte percentage was calculated as the percentage of total granulocytes which were macrogranulocytic. The reasons for this classification and its significance will be discussed later.

In some cases blood volumes were estimated by the T-1824 method which has been described in two previous reports.[1, 2] A planned schedule of treatment was followed in each case. Hematological studies of blood and bone marrow and blood volume studies were performed as often as indicated, or as often as was possible during the conduct of the case. Initially, these included plasma bilirubin, direct and indirect Coombs test, and resistance of the red cells to hypotonic solutions.

Most patients were placed on a Spies low-folic-acid, low-protein diet.[3] This was not always well accepted as patients often found it too dry and tasteless. Further laboratory investigations of gastric acidity, liver function, glucose tolerance, urobilinogen excretion, and stool fats were done in many cases. Some rebelled against the strict regime and the frequent hematological studies. Cases are included in this study only if a definite megaloblastic change could be detected in the initial bone marrow and if subsequent studies were adequate.

Materials

Both the amorphous and the crystalline B_{12} (Squibb) were used and no difference could be detected between them. Pteroylglutamic acid (Lederle) and *Leuconostoc citrovorum* factor, or folinic acid (Lederle), were used in many cases. A little oral iron was tried but in order to determine the exact amount of iron absorbed, intravenous saccharated iron oxide (Smith, Kline & French) was often used and was given in doses of 50 to 200 mg. daily. The average dose was 100 mg. two to three times a week. Where stated, a high-protein diet was prescribed with the assistance of the diet dispensary.

Case Reports

CASE 1, A.—J. U. (Fig. 1.)

History.—A 32-year-old housewife was admitted May 31, 1948, in the eighth month of her seventh pregnancy, complaining of vomiting, increasing fatigue, pallor, faintness, and dyspnea on slight exertion, and soreness of the mouth, all of which had been present for about two weeks. Her six preceding pregnancies were normal except for postpartum hemorrhage after the fifth. There was no previous history of anemia. Her economic circumstances were very poor and her diet was grossly inadequate in animal protein, fruit, and green vegetables.

Physical Examination.—The patient was a very pale, slightly obese pregnant woman. The tongue was smooth. There were old and recent retinal hemorrhages and the liver was palpable 3 cm. below the right costal margin.

Laboratory Findings.—The hemoglobin 12 days before admission was 10.3 Gm. per cent. On admission it had fallen to 3.1 Gm. per cent, the red blood count was 1.18 million and the white blood count was 2,800. Blood smears showed a marked variation in size and shape of the red cells, many microcytes, a number of macrocytes, a rare myelocyte, a definite lymphocytopenia, and a number of hypersegmented large neutrophils. Sternal bone marrow aspiration the day after admission showed a hyperplastic marrow with many islands of promegaloblasts, and basophilic megaloblasts, frequent multipolar mitoses,

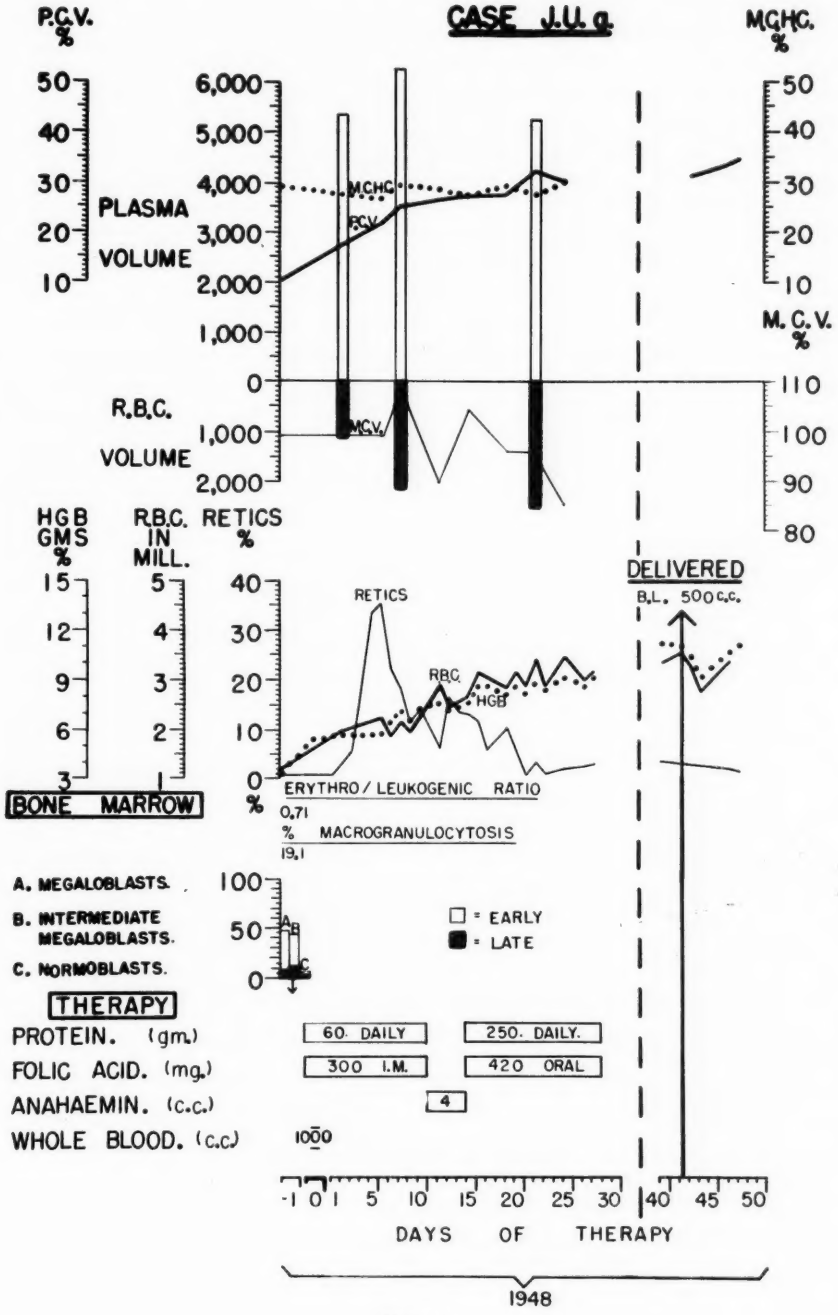


Fig. 1.

numerous macrogranulocytes and macropolycytes; 93 per cent of the nucleated red cells were megaloblasts and intermediate megaloblasts; 19.1 per cent of the granulocytes were macrogranulocytic. Total serum protein was 5.04 Gm. per cent, with albumin 3.12 and globulin 1.92; serum bilirubin was 0.4 mg. per cent.

Course and Therapy.—On the first two days after admission she received 1,000 c.c. of whole blood. Fig. 1 shows the remainder of the therapy which consisted of folic acid intramuscularly. There was a marked reticulocyte response on the sixth day of treatment with folic acid. The blood smear at this time showed well-marked polychromatophilia, basophilia, and stippling of the red cells with many Cabot rings, Howell-Jolly bodies, polychromatic and orthochromatic normoblasts, and the red cells were predominantly macrocytic. Sternal bone marrow aspiration on the seventh day showed reversion toward normoblastic erythropoiesis, although this was not complete. Subsequently, concentrated liver extract was given for four days and a slight secondary reticulocytosis developed. She was then placed again on folic acid and the protein intake was increased to 250 Gm. daily. Gastric analysis showed hypochlorhydria after histamine. She was discharged from the hospital and readmitted twelve days later with a hemoglobin of 11.2 Gm. per cent. She was delivered spontaneously, with a moderate postpartum hemorrhage estimated at 500 c.c. She was discharged nine days after delivery with a hemoglobin of 11.1 Gm. per cent and continued to take folic acid for one month after returning home.

It has long been our belief that the reticulocytes which appear as a result of liver or other specific therapy are young cells and that they remain functional in the circulating blood. Blood volume determinations were performed on the second treatment day and two days after the first reticulocyte peak. Although the hemoglobin concentration rose only from 5.6 Gm. per cent to 7.0 Gm. per cent during this period, the total blood volume increased from 6,423 ml. to 8,434 ml. and the red-cell volume almost doubled, increasing from 1,118 ml. to 2,184 ml.

The total hemoglobin increased at the same time from 359 to 590 Gm. Thus, the striking increase of total circulating red cells and hemoglobin was masked by the concomitant increase of plasma volume. Although the red-cell volumes rose by 12.4 per cent to 2,557 ml. in the two weeks between the second and third blood volume determinations, the total blood volume decreased to 7,820 ml. due to a 1,000 ml. decrease of plasma volume. The 27 per cent increase of hemoglobin concentration to 8.9 Gm. per cent was due in part to this diminution of plasma volume.

Comment.—This patient had a severe megaloblastic anemia in the eighth month of pregnancy with a history of dietary deficiency and without complicating infection. The drop of hemoglobin from 10.3 Gm. per cent to 3.1 Gm. per cent in the twelve days preceding admission and in the absence of apparent bleeding would suggest the presence of a hemolytic component. Hematological findings in blood and bone marrow responded initially to folic acid and this was followed by a moderate secondary response of reticulocytes to parenteral refined liver extract. Increase of both plasma and red-cell volume masked the extent of initial response of the blood.

CASE 1, B.—J. U. (Figs. 2, 3, 4, and 5.)

History.—This patient was next seen in the obstetrical clinic on the eighteenth of May, 1949, 5½ months pregnant, with a hemoglobin of 9.8 Gm. per cent. In the seventh month she developed a cellulitis of both feet and both ankles which cleared with conservative management. She became very tired after this and developed a furuncle of the breast, which made it necessary to admit her during the eighth month for penicillin treatment. She said that she had vomited persistently until the sixth or seventh month. Her diet again had been poor, consisting largely of bread and potatoes.

Physical Examination.—She was an obese woman who had gained 70 pounds during this pregnancy. The liver and spleen were not enlarged. The tongue was smooth with fissuring of the angles of the mouth. Neurological examination was normal. There were no retinal hemorrhages.

Laboratory Findings.—On admission the hemoglobin was 8.1 Gm. per cent, red blood count 2.88 million, mean corpuscular volume 96 cu. microns, mean corpuscular hemoglobin concentration 29 per cent, and white blood count 8,000. The anemia was dimorphic with many microcytes and macrocytes, with moderate anisocytosis, poikilocytosis, basophilic stippling, basophilia and polychromatophilia of the red cells. On August 30 she was given a transfusion of 350 c.c. of whole blood. A sternal marrow aspiration on that date showed a few classical megaloblasts, 87 per cent intermediate megaloblasts, 9.8 per cent macrogranulocytes, and

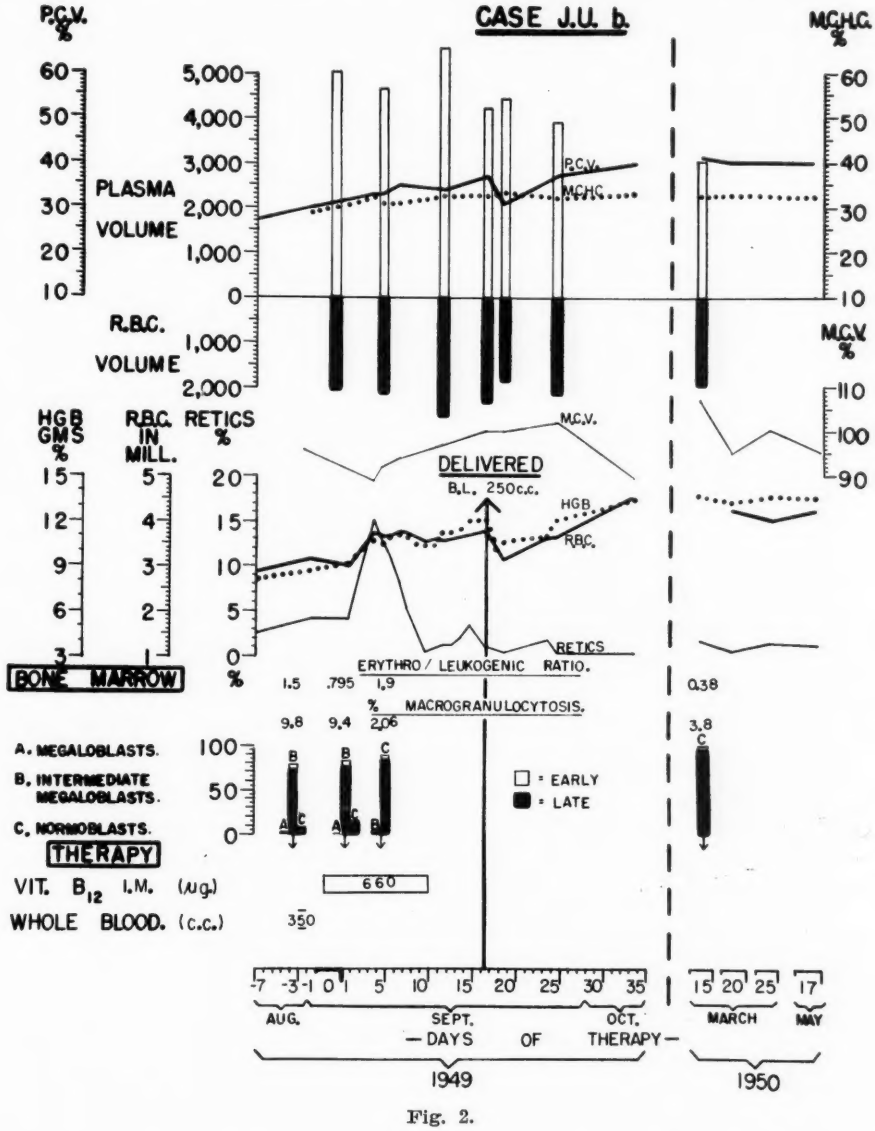


Fig. 2.

relative erythropoietic hyperplasia. The majority of the nucleated red cells approached closely the classical megaloblast morphologically but had not quite completed these cytological alterations and consequently were classified as intermediate megaloblasts. Gastric analysis showed small amounts of free hydrochloric acid after histamine.

Course and Therapy.—She was given 60 Gm. of protein daily and on September 2, seventeen days before delivery, intramuscular vitamin B_{12} was begun. The day after treat-

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 3.—(Case 1, B, J. U.) Promegaloblasts and basophilic megaloblasts before treatment with vitamin B_{12}. (×1130; reduced ⅓.)

Fig. 4.—(Case 1, B, J. U.) An intermediate promegaloblast and intermediate megaloblasts 24 hours after first injection of vitamin B_{12}. (×1130; reduced ⅓.)

Fig. 5.—(Case 1, B, J. U.) Normoblastic erythropoiesis 5 days after first injection of vitamin B_{12}. Note nonphagocytic reticulum cell. (×1130; reduced ⅓.)

ment was started the bone marrow had not changed significantly, and after four days the reticulocytes rose to 15 per cent. The hemoglobin was then 10.8 Gm. per cent, red blood count 3.72 million, and the white blood count 13,500. The next day sternal puncture showed an almost complete reversion of the bone marrow to normoblastic erythropoiesis. The true extent of the postreticulocytosis increase of hemoglobin and red cells was again masked by a concomitant rise of both red cell and plasma volume. She was delivered spontaneously with a normal blood loss and the next morning the Fallopian tubes were ligated. The remainder of the puerperium was uneventful and she left the hospital eighteen days after delivery with a hemoglobin of 13.3 Gm. per cent and red blood count of 4.53 million. She returned for recheck six months later when a bone marrow aspiration was normal and hemoglobin and red cell findings compared favorably with the findings at discharge. She appeared to be in good health, and a ventral hernia was repaired.

Comment.—In her eighth pregnancy this patient developed megaloblastic anemia which responded to folic acid. The anemia recurred in this, her ninth pregnancy. Because of her past history she was observed more carefully ante partum and the anemia was detected much earlier. Her diet was inadequate in both pregnancies. Complicating infection, absent in the preceding pregnancy, was present in this one. On this occasion hematolcgical findings in blood and bone marrow responded to parenteral administration of vitamin B_{12}. A postreticulocytosis rise of plasma as well as of red-cell volume concealed the true extent of hemoglobin and red-cell increase.

CASE 2.—G. M. (Fig. 6.)

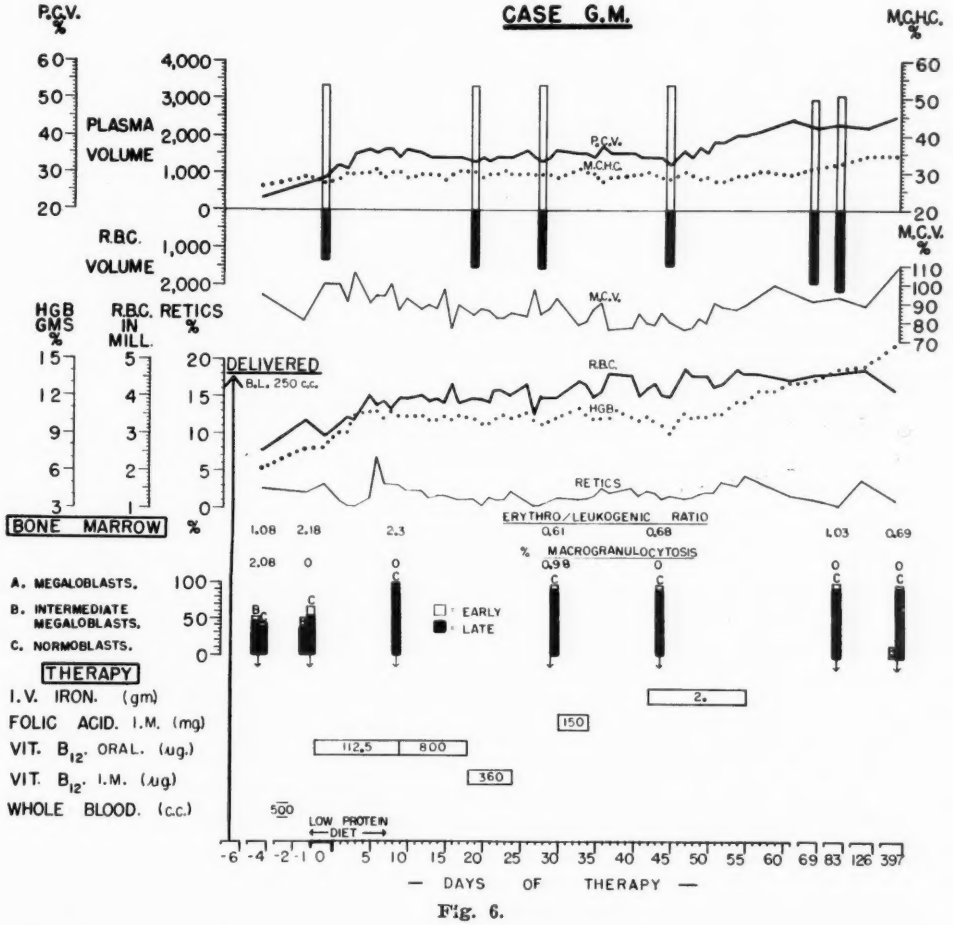


Fig. 6.

History.—This 29-year-old woman was first seen two days after delivery. She had a moderate blood loss; the fetus had died in utero some time previously. The pregnancy had been normal throughout and she felt well. Her diet was stated to have been adequate. She had had a miscarriage and curettage three years earlier with some anemia for which she was given iron and liver.

Physical Examination.—A slightly obese woman, she was apparently well except for the recent delivery. The tongue was normal and the spleen was palpable 3 cm. beneath the left costal margin. Neurological examination was normal. The blood pressure was 120/100.

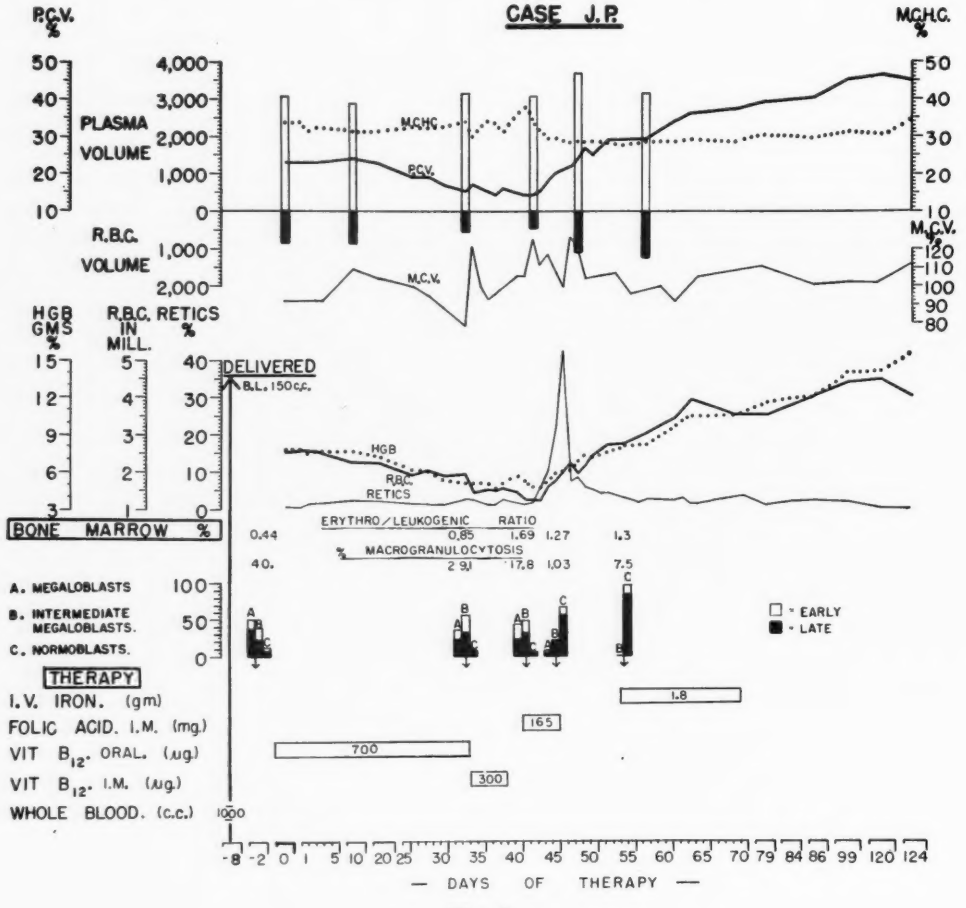


Fig. 7.

Laboratory Findings.—The postpartum hemoglobin was 6.2 Gm. per cent, red blood count was 2.53 million, mean corpuscular volume 94 cu. microns, mean corpuscular hemoglobin concentration 26.3 per cent, reticulocytes 2.5 per cent. The red cells showed anisocytosis and poikilocytosis with many hypochromic microcytes and a few macrocytes. She was given a transfusion of 500 c.c. of whole blood which raised the hemoglobin to 7.8 Gm. per cent. Sternal puncture before and after transfusion showed erythropoietic hyperplasia with 55 per cent intermediate megaloblasts and only 2 per cent macrogranulocytes. Gastric analysis showed achlorhydria refractory to histamine. The Coombs test was negative. Liver function tests were normal, and the total protein was 6.75 Gm. per cent with normal albumin-globulin ratio. The glucose tolerance curve and plasma bilirubin were normal. The stools did not contain excessive fat.

Course and Therapy.—She was placed on a low-protein Spies diet. Oral vitamin B_{12} produced improvement in the bone marrow and peripheral blood and a reticulocyte peak

of 6.8 per cent on the sixth day. Intramuscular vitamin B_{12} and later intramuscular folic acid were given with no additional hematological response. Intravenous saccharated iron oxide was administered to a total of 2 Gm. A sustained reticulocytosis and steady rise of hemoglobin and red blood cells resulted; twenty-six days after beginning this treatment the hemoglobin was 13.3 Gm. per cent and the red blood count 4.6 million. A month later the hemoglobin was 14.5 Gm. per cent and the red blood count 4.7 million. She was seen a year later when the findings showed no anemia but it was noted that an occasional megaloblast of intermediate type was seen in the bone marrow.

Comment.—This patient had a moderately severe anemia. Intermediate megaloblasts were numerous in the bone marrow, but macrogranulocytes were scanty. In the absence of infection and dietary deficiency, gastric achlorhydria would suggest the etiological possibility of gastric intrinsic factor deficiency. Her anemia responded to oral administration of vitamin B_{12} in dosage unlikely to have produced remission of Addisonian pernicious anemia in relapse, 12.5 μg. daily. This response may be considered as evidence against a deficiency of gastric intrinsic factor.

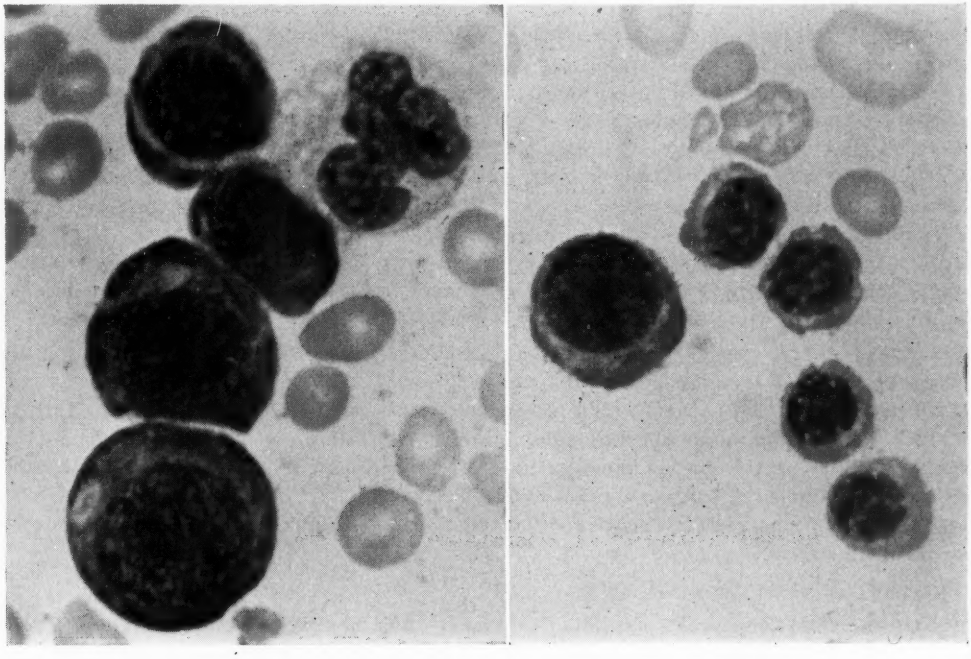


Fig. 8. Fig. 9.

Fig. 8.—(Case 3, J. P.) Promegaloblast, megaloblasts, and macrostab before vitamin B_{12} treatment. (×2,300; reduced 2/7.)

Fig. 9.—(Case 3, J. P.) Seventy-two hours after first injection of folic acid, all normoblasts showing many transitional changes toward megaloblasts. (×2,300; reduced 2/7.)

CASE 3.—J. P. (Figs. 7, 8, and 9.)

History.—A 19-year-old woman was admitted April 10, 1950, in her second pregnancy and delivered spontaneously with a normal blood loss. Seven days later a hematological consultation was requested. She had been well during pregnancy and had a fairly adequate diet until the last two months when her gums became so sore that she could not eat solid food and she was sustained solely by eggnogs. She lost about 10 pounds in weight during this time. Two years earlier she had had an incomplete abortion and the hemoglobin following this was normal.

Physical Examination.—She was a very thin, pale woman whose tongue was raw and beefy and who had a marked gingivitis with slight fissuring of the angles of the mouth. There were no other abnormal findings.

Laboratory Findings.—Just before admission the hemoglobin was 8.6 Gm. per cent; immediately following delivery it dropped to 5.6 Gm. per cent and she was given 1 L. of whole blood. Seven days post partum the hemoglobin was 7.8 Gm. per cent, the red blood count was 2.5 million, the red cells were mainly microcytic and hypochromic with some macrocytes present. Sternal puncture showed 90 per cent megaloblasts and intermediate megaloblasts and 40 per cent macrogranulocytes. Liver function tests were normal. Serum protein was 6.0 Gm. per cent with normal albumin-globulin ratio; gastric analysis showed free acid after histamine. Stool analysis showed normal fat absorption.

Course.—Following delivery she received 1 Gm. of oral ferrous sulfate daily for one week. She was then placed on a Spies low-protein diet and given 12.5 μg. of vitamin B_{12} daily by mouth. She insisted on leaving the hospital and was followed at home where her diet was very low in protein. After 26 days the dose of vitamin B_{12} was increased to 100 μg. daily for seven days and then 60 μg. was given parenterally every day for five days. Her condition deteriorated steadily, she complained of weakness and breathlessness, the hemoglobin fell to 4.8 Gm. per cent, and the red blood count to 1.23 million, during this period the hematocrit and total red cell volume decreased and the anemia became hyperchromic and macrocytic. The bone marrow was still profoundly megaloblastic, and the erythrogenic-leukogenic ratio steadily increased, indicating relative erythroid hyperplasia. She was readmitted to the hospital and 165 mg. of folic acid was given intramuscularly over a six-day period. Reticulocytosis of 42 per cent developed five days after folic acid was begun and was followed by a rapid increase of hemoglobin and red cells. As in Cases 1, A and 1, B, the reticulocyte peak was followed by an increase of plasma as well as red-cell volume, which partially concealed the true rise of hemoglobin and red cells. The bone marrow appeared nearly normal. The red cells became hypochromic and 1.8 Gm. of saccharated iron oxide was given intravenously which, after one month, led to a hemoglobin of 12 Gm. per cent and after two months to a hemoglobin of 14 Gm. per cent. Her diet was poor during this whole period. One year later she was in good health.

Comment.—This patient subsisted almost entirely on eggnogs during the last two months of pregnancy. Her tongue, gums, and the angles of the mouth showed evidence of nutritional deficiency. Her megaloblastic anemia was severe and deteriorated for thirty-eight days post partum while she was given oral ferrous sulfate and oral and intramuscular vitamin B_{12}. During this period the anemia was hyperchromic and macrocytic. Folic acid produced a profound clinical and hematological response; the blood then developed evidence of iron deficiency which subsequently responded to saccharated iron oxide administered intravenously.

CASE 4.—Y. G. (Figs. 10, 11, 12, and 13.)

History.—This 21-year-old gravida ii housewife was admitted to the hospital May 17, 1950, in the beginning of the ninth month of pregnancy. For two months she had suffered severe nausea and vomiting. The vomitus occasionally contained blood streaks. She also complained of headache, swelling of the legs, sore tongue, fatigability, epigastric distress, frequent micturition, and occasional loose stools. Her diet had been deficient in animal protein with practically no milk, one egg per week, fish once weekly, and occasionally a small amount of chicken. Potatoes were her principal vegetable. The past history was irrelevant.

Physical Examination.—She was chalky pale. Her tongue showed some atrophy of the lingual papillae. There was slight ankle edema. The blood pressure was 130/78. There were no other positive signs.

Laboratory Examination.—The urinalysis showed a slight trace of albumin; gastric analysis showed free hydrochloric acid present. Total fat in the stool was 14.8 per cent (72 hour Schmidt diet); the 24 hour urinary urobilinogen was 10.5 mg. per cent (0-9 ml). Total serum protein was 5.88, albumin 3.41, globulin 2.47. Plasma bilirubin: total 1.0 mg. per cent, direct 0.43 mg. per cent. Liver flocculation tests were negative, the nonprotein nitrogen was 18.5 mg. per cent. Glucose tolerance was: fasting 93, 30 minutes 99, 1 hour 111, 2 hours 103. The Coombs test was negative.

Course in Hospital.—On admission the hemoglobin was 9.4 Gm. per cent, red cells 2.24 million, mean corpuscular volume 106 cu. μ. The smear showed anisocytosis and poikilocytosis, many large macrocytes, some microcytes and an occasional macropolycyte. The red-cell volume was 1,329 ml., 82 per cent of nucleated red cells of the bone marrow were megaloblasts, and 43.9 per cent of the granulocytes were macrogranulocytes. Two days after admission she delivered fraternal twins, the second one as a breech with an estimated blood loss of 800 ml. for which she was given a transfusion of 500 ml. of blood. On the same day she was given 120 μg of vitamin B_{12} intramuscularly; 8 days post partum she received 60 μg. of vitamin B_{12}. There was no apparent response to vitamin B_{12} over a twelve-day period. Subsequently, she was given folic acid, 30 mg. daily intramuscularly for seven days. Two days later the reticulocytes rose to 9 per cent and subsequently the red cells and hemoglobin increased. Twenty-five days after the first injection of folic acid the bone marrow was almost completely normoblastic. Later, she developed a mild iron deficiency which responded to the intravenous administration of 1.2 Gm. of saccharated iron oxide.

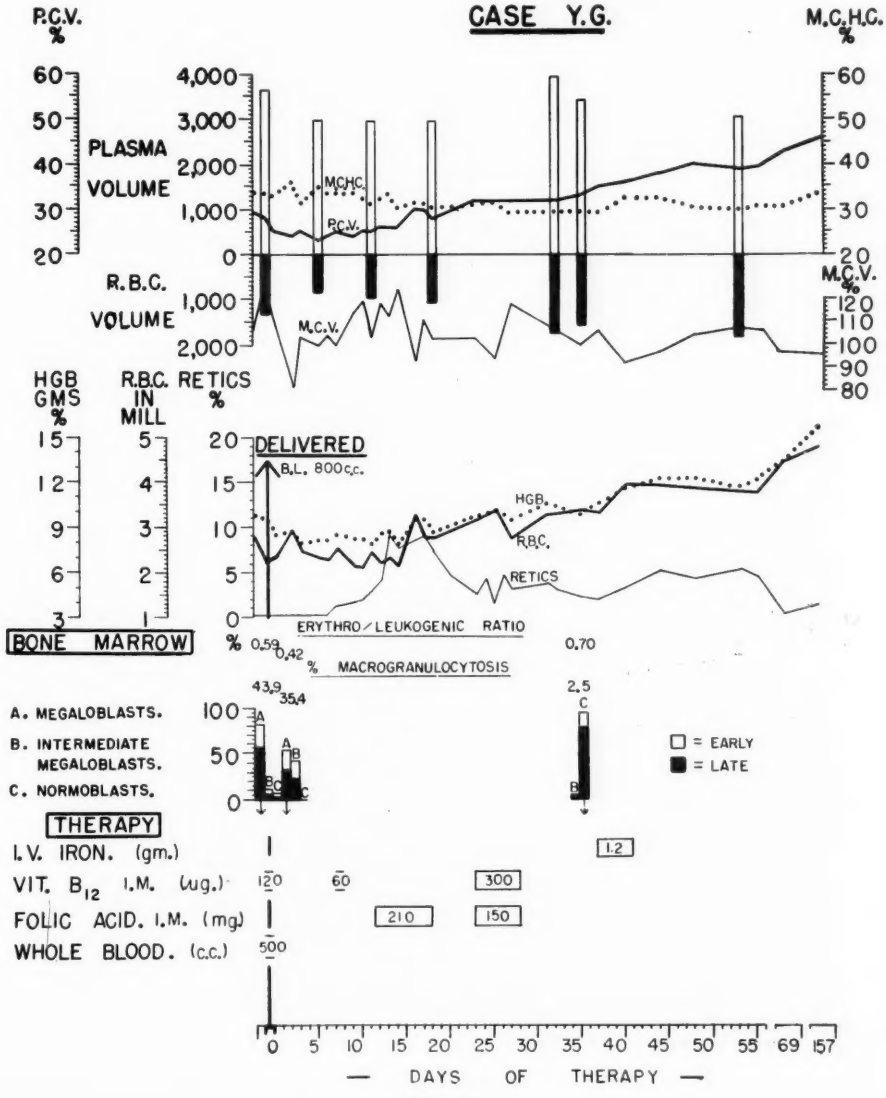


Fig. 10.

Fig. 11. Fig. 12. Fig. 13.

Fig. 11.—(Case 4, Y. G.) Before vitamin B_{12} and transfusion, promegaloblast, proerythroblast, basophilic megaloblasts, and 3 macrostabs. (×2,300; reduced ⅔.)

Fig. 12.—(Case 4, Y. G.) Before vitamin B_{12} and transfusion, 2 promegaloblasts, 2 polychromatophilic megaloblasts. (×2,300; reduced ⅔.)

Fig. 13.—Case 4, Y. G.) Twelve days after first folic acid injection and before intravenous iron administration, normoblastic erythropoiesis. Note the reduced ratio of cytoplasm to nucleus. (×2,300; reduced ⅔.)

Comment.—It is unlikely that there was any response to the first injection of vitamin B_{12}. The subsequent response could have been due either to the second injection of vitamin B_{12} or to folic acid, or both. The rise of reticulocytes and also of red cells occurred rather early for a pure folic acid effect. There was no secondary response after a further course of vitamin B_{12} and folic acid.

CASE 5.—K. B. (Figs. 14, 15, and 16.)

History.—This 28-year-old gravida iii was first seen in the clinic July 18, 1950, in the fifth month of pregnancy. She complained of dizziness and fatigue. The intake of protein and milk were inadequate throughout her pregnancy. She was placed on ferrous sulfate, 5 grains three times a day after meals. Her first pregnancy was complicated by pre-eclampsia. After delivery of her second child she developed puerperal pyelitis, virus pneumonia, and intrauterine infection.

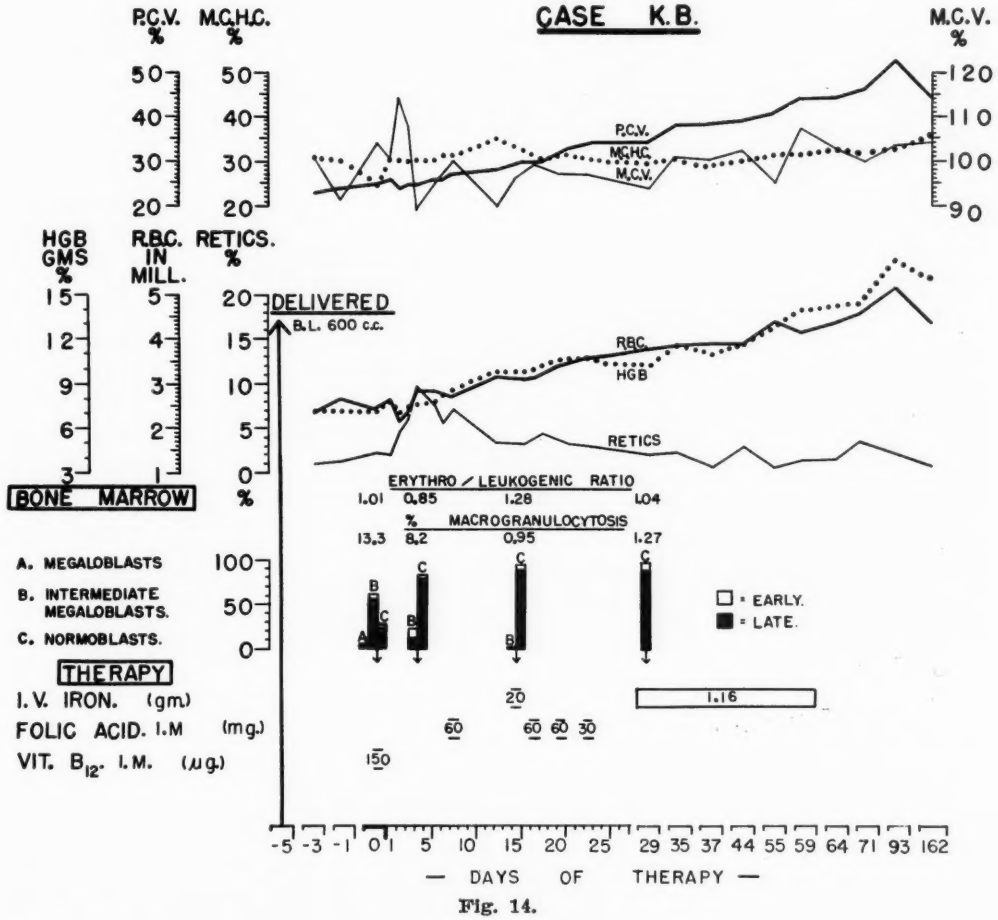


Fig. 14.

Physical Examination.—The blood pressure was 130/60. She appeared somewhat underweight, haggard and pale. Otherwise there were no abnormalities.

Laboratory Findings.—The nonprotein nitrogen was 30.8 mg. per cent. Total protein was 6.38, albumin 3.65, globulin 2.7 Gm. per cent; plasma bilirubin, direct 0.25 mg. per cent, indirect 0.4 mg. per cent; cephalin cholesterol flocculation negative; thymol turbidity, 3.3 units; thymol flocculation negative; A.C. and P.C. blood sugar normal; normal quantitative stool and urine urobilinogen excretion. Gastric analysis showed ample free hydrochloric

acid. The direct and indirect Coombs test was negative. Hematological study on July 23 showed the red blood count 3.61 million, hemoglobin 12.0 Gm. per cent, mean corpuscular volume 97 cu. μ, mean corpuscular hemoglobin concentration 34 per cent, a few macrocytes and an occasional macropolycyte.

Course.—On November 9, she delivered a 4,240 gram healthy baby with an estimated blood loss of 300 ml. From the fourth to the twelfth day post partum she had a mild endometritis with the temperature rising as high as 101.8° F. This infection apparently responded to penicillin and streptomycin. Hematological study 2 days post partum showed the red blood count to be 2.38 million, hemoglobin 7.0 Gm. per cent, hematocrit 23 per cent, mean corpuscular volume 100 cu. μ, and mean corpuscular hemoglobin concentration 30.4 per cent. Bone marrow aspiration on November 14, 5 days post partum, showed increased cellularity, increased erythrogenic-leukogenic ratio, macrogranulocytes 13.3 per cent, megaloblasts 4 per cent, intermediate megaloblasts in all stages of maturation, 65

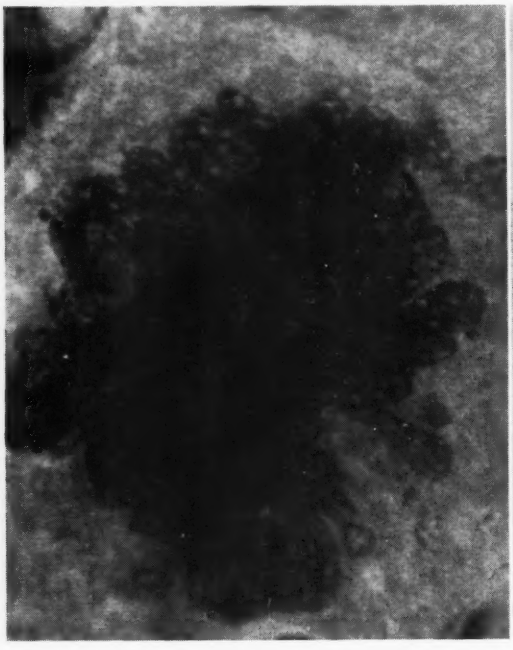


Fig. 15.

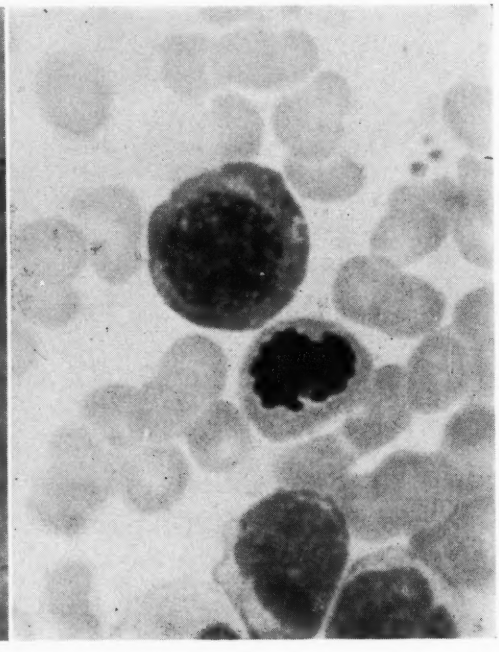


Fig. 16.

Fig. 15.—(Case 5, K. B.) Before vitamin B_{12} therapy, atypical megakaryocyte showing multiple lobulation of nucleus. (×2,300; reduced 2/7.)

Fig. 16.—(Case 5, K. B.) Before vitamin B_{12} administration, late intermediate megaloblast, atypical mitosis of well-hemoglobinated nucleated red cell. (×2,300; reduced 2/7.)

per cent. She was given one injection of 150 μg of vitamin B_{12} intramuscularly. Four days later the reticulocytes had risen to 9.6 per cent and the bone marrow showed a sharp decrease of macrogranulocytes and megaloblasts. Eight days after vitamin B_{12} administration, the hematological values had risen, with the red blood count 2.72 million, hemoglobin 8.6 Gm. per cent, and hematocrit 27 per cent. No significant secondary reticulocytosis occurred. The bone marrow, however, showed significant change toward normal. Folic acid, 60 mg. intramuscularly, was given, and an additional 150 mg. folic acid was administered during the next two weeks. Hemoglobin and red-cell values continued to increase but the hemoglobin rise began to lag behind the red-cell increase; the mean corpuscular hemoglobin concentration decreased to 30 per cent and the red cells developed some central pallor. The bone marrow findings were completely normal. Intravenous iron, 1.16 Gm. was administered with resultant satisfactory return of hematological values to normal.

Comment.—The presence of a few macrocytes, the occasional macropolycyte, and slight elevation of the mean corpuscular volume in the fifth antepartum month may well have been due to beginning development of megaloblastic anemia. Ante partum, there was no apparent response to oral iron. Immediately post partum she was found to have a well-developed megaloblastic anemia. Her diet had been deficient in protein. The megaloblastic anemia responded to vitamin B_{12} intramuscularly in the presence of puerperal endometritis. There was no secondary detectable response to folic acid. Iron deficiency became apparent subsequently and responded to intravenous iron.

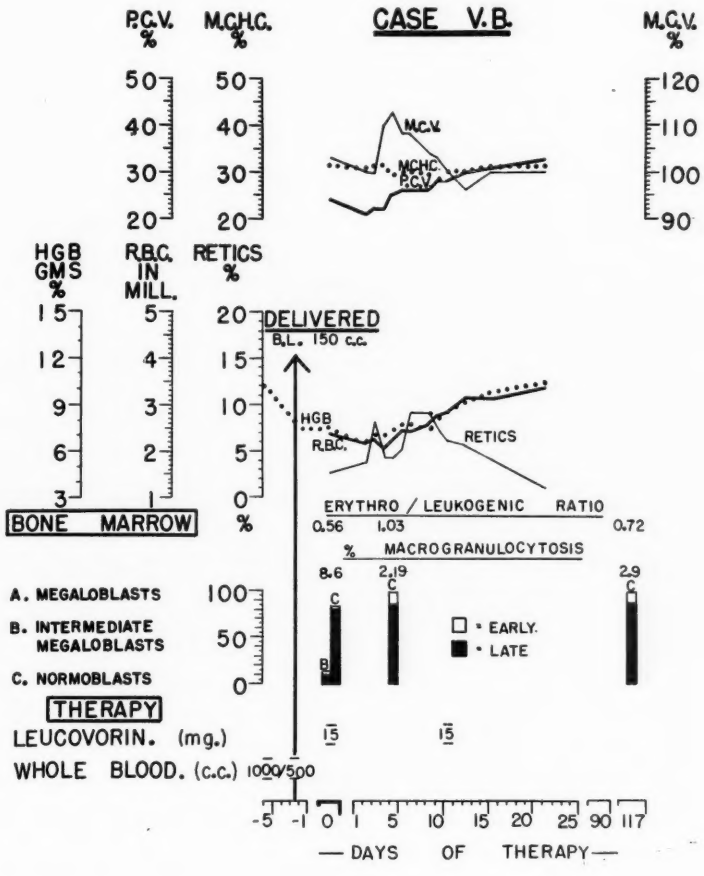


Fig. 17.

CASE 6.—V. B. (Fig. 17.)

History.—This 37-year-old woman was admitted on Nov. 19, 1951, at the beginning of the ninth month of her thirteenth pregnancy. Headache and occasional dizziness were her only complaints. She had had rheumatic fever at the age of 12 years; toxemia of pregnancy in 1941 with a premature stillbirth, a blood pressure of 165/110, a 3 plus albuminuria, and postpartum thrombophlebitis with postpartum hemoglobin determinations of 9.0 Gm. per cent and 10.0 Gm. per cent; pre-eclamptic toxemia again in 1943, 1947, and 1950, with edema, elevated blood pressure, and albuminuria in each pregnancy. The hemoglobin was normal when observed between pregnancies; moderate anemia occurred in at least three pregnancies associated with pre-eclampsia. Thrombophlebitis again developed post partum in 1947.

Physical Examination.—The blood pressure was 210/110 (eight weeks previously it had been 142/88). There were no other abnormalities.

Laboratory Findings.—On November 19 the nonprotein nitrogen was 28.4, uric acid 8.5, total proteins 5.85, albumin 3.01, globulin 2.84. Liver flocculation tests were normal. Urinalysis showed albumin 3 plus, specific gravity 1.004.

Course.—After induction of labor she was delivered on November 22, with an estimated blood loss of 150 ml. The premature baby lived four days. Ante partum, she lost about a pint of blood from vaginal bleeding and was given a transfusion of 1,000 ml. of blood. Another 500 ml. of blood was given at the time of delivery. Post partum, the blood pressure remained elevated; the lowest reading was 140/90 and a slight albuminuria persisted. In spite of the transfusions the hemoglobin dropped from 10.2 Gm. per cent ante partum to 7.3 Gm. per cent post partum; at this time the red blood count was 2.36 million, mean corpuscular volume 103 cu. μ, mean corpuscular hemoglobin concentration 31.5 per cent. The bone marrow showed 13 per cent intermediate megaloblasts and 8.6 per cent macrogranulocytosis. Administration of 15 mg. of Leucovorin was followed by disappearance of the intermediate megaloblasts, decrease of macrogranulocytes, and increase of reticulocytes, hemoglobin, hematocrit, and red cells. A second dose of 15 mg. produced no obvious effect.

Comment.—This patient had severe pre-eclamptic toxemia of pregnancy for which labor was induced prematurely. Three days ante partum the hemoglobin did not reveal the underlying megaloblastic anemia which must have been present. Although she received approximately three times the estimated total blood loss by transfusion, anemia developed rapidly, suggesting the presence of a hemolytic component, or inaccurate estimation of blood loss. The transfusion of 1,500 ml. may have partially masked the bone marrow megaloblastosis. The hematological findings would indicate that there was some response to folinic acid.

Clinical and Laboratory Features

There were no pathognomonic or typical symptoms. Four of the patients were primiparas and 14 were multiparas. The youngest was 19 years of age, the oldest was 38 years of age: the average age was 26.2 years. The anemia was detected ante partum in 9 patients and post partum in 9 patients.

Twelve patients had a deficient intake, usually of animal protein and fruit and often of green vegetables, especially fresh vegetables. The dietary history of 2 patients was said to be satisfactory, although details were not listed. The dietary history of 4 patients was not detailed.

Five patients had excessive vomiting in the second and/or the third trimester. Thirteen patients had no excessive vomiting. Diarrhea was a minor symptom in 3 patients and absent in 15 patients.

One patient developed pyelitis during pregnancy, one had a cellulitis of the foot and great toe and a large furuncle of the breast at the time of admission, one had acute pharyngitis and bronchitis, and one had stomatitis and gingivitis. There were no other significant antepartum infections.

Two patients complained of sore mouth or tongue. These symptoms were absent in 16 patients.

Fourteen patients complained variably of excessive fatigue. None noted air hunger on exertion or other symptoms of severe anemia, although physical performance was obviously limited in several of the cases of marked anemia.

On physical examination, the majority seemed underweight, one patient was overweight. Three patients were mildly edematous: one patient had moderate unilateral edema due to varicose veins; one patient, in congestive heart failure from rheumatic heart disease, was severely edematous. Smoothness of the tongue with some atrophy of lingual papillae was present in 6, or one-third of the patients; ulcers of the tongue were present in one patient; 2 patients had gingivitis and 2 had well-defined perlèche. Pallor varied with the severity of the anemia. Hypertension was mild in one patient and severe in the one patient of the series who suffered pre-eclampsia. Nail changes, such

as koilonychia were not observed in any patient. One patient had retinal hemorrhages. The spleen was palpable 2 cm. beneath the left costal margin in one patient. The liver was palpably enlarged in 3 patients and normal in 15 patients. Neurological examination was normal in every instance. There was no icterus.

Slight albuminuria was recorded in 2 instances; the pre-eclamptic patient had severe albuminuria; 15 patients had no albuminuria. Liver function tests showed slight impairment in 3 patients, moderate impairment in the patient with pre-eclampsia, and were normal in 4 patients. Three patients had decreased plasma albumin; plasma proteins were normal in 8 patients. One patient had a slight impairment of glucose tolerance (146 mg. per cent at end of two hours). None showed evidence of decreased absorption of glucose. Fat balance studies in two patients were normal. The stools of most of the remaining patients were stained with sudan III and none showed excessive amounts of microscopic fat. Gastric analysis using histamine was performed in 10 patients; one was achlorhydric, 2 were hypochlorhydric, and acidity was normal in 7 patients. One patient had a borderline plasma bilirubin of 1.0 mg. per cent; there was no other evidence of hyperbilirubinemia. Quantitative studies of urobilinogen excretion in urine and stool were normal in the 4 patients studied. Four patients were Rh negative and 14 were Rh positive; none exhibited isoimmunization or gave birth to babies with hemolytic disease.

Two patients had mild bleeding and one had moderate bleeding ante partum. Five of the infants were premature, one was stillborn, one died four days after birth and there was one set of healthy twins. Post partum 2 patients developed acute pyelitis and 3 had puerperal endometritis. The estimated blood loss varied at delivery from 100 to 800 ml.; in 11 patients it was estimated at less than 300 ml.; in 5 patients at 300 to 500 ml., and in 2 patients, at 800 ml. The average was 340 ml.

In the earlier part of this study megaloblastic anemia was detected more frequently than later on. As clinicians and social service workers became more familiar with the syndrome as a result of seminars and case presentations at ward rounds, prophylactic dietary instructions and use of polyvitamin supplements increased. From early in 1953 until the present, not one case of megaloblastic anemia associated with pregnancy and the puerperium was detected, although hematological screening was consistently applied. For a number of years, it has been customary to prescribe 3 tablets daily of a proprietary supplement. Each tablet of this supplement contains 0.2 Gm. of ferrous sulfate and, in June of 1945, 50 mg. of ascorbic acid was incorporated in each tablet. In June, 1953, 1.0 μg of vitamin B_{12} and 1.0 mg. of folic acid were incorporated in each tablet. The failure to detect this syndrome since then may have been due to the supplementary intake of one or both of these substances.

Initial Hematological Findings in Blood and Bone Marrow

Initial examination of the blood showed no constant findings. All combinations of macrocytosis, normocytosis, microcytosis, and of hypochromia, normochromia, and hyperchromia were observed. In 10 patients initial hypochromia of the red cells suggested some degree of iron deficiency. Two patients had a hypochromic microcytic anemia, 4 hyperchromic macrocytic, and 6 had a so-called dimorphic anemia with both hyperchromic macrocytes and hypochromic microcytes present in considerable numbers. Two were normochromic and macrocytic and two were normochromic and normocytic. Careful examination of the differential smears provided more helpful diagnostic

clues than did the quantitative figures. Thus, with the exception of smears from 2 patients, from a few to many well-hemoglobinated macrocytes and/or megalocytes could be found. Megaloblasts or intermediate megaloblasts were found in the smears of 3 patients; macrogranulocytes in the form of large hypersegmented neutrophils, giant stabs, and/or macrometamyelocytes were present in the smears of 7 patients. The presence of megaloblasts and macrogranulocytes permits a presumptive diagnosis from the blood findings alone.

In 3 patients (Cases 1, A, 3, and 6) hemoglobin and red-cell values decreased rapidly before effectual therapy was given, suggesting the presence of a hemolytic component.

Bone Marrow Changes

Generally, the marrow particles showed some increase of cellularity involving megakaryocytes, white cells, and nucleated red cells. In both the supravital preparations and the smears of marrow particles some, but not all, of the initial samples exhibited increased numbers and phagocytic activity of the reticulum cells for both pigment and red-cell fragments, suggesting increased destruction of the red cells. Plasma cells seemed increased in the samples, especially in the region of reticulum cells.

The initial erythrogenic-leukogenic ratio varied from 0.32 to 1.5 with a mean average of 0.66, which is not significantly greater than found in the nonpregnant or postpartum normal. In only 3 of the 18 cases was the initial ratio below 0.5.

Although the degree of megaloblastic changes and the number of megaloblasts present paralleled the severity of the anemia in general, it was impossible to establish this correlation in a considerable number of initial marrow studies. Thus, classical megaloblasts were not present in any of the 4 patients with red-cell counts of greater than 3.5 million and were present in half of the patients with counts of below 3.5 million; they were absent in 3 patients with initial red-cell counts of less than 2.5 million and were present in 3 patients with counts of from 2.5 to 3.5 million. Intermediate megaloblasts were present in all 19 cases and macrogranulocytes were present in 18 marrows of the 19 cases of this anemia. Nor did the degree of macrogranulocytosis always parallel the degree of megaloblastosis. High percentages of macrogranulocytes were present in some marrows in which only a few intermediate megaloblasts were found (e.g., patients W. S., M. Ros., F. B., and C. G.) and in other instances (Patients G. M. [Case 2] and E. S.) there were large numbers of intermediate megaloblasts with only a few macrogranulocytes. Cells showing all degrees of transition between typical normoblasts and typical megaloblasts were observed in all stages of maturation and were classified as intermediate megaloblasts. A certain degree of megaloblastic transition was usually predominant in a given marrow preparation, although a varying proportion of typical normoblasts was invariably present. Morphological changes of cytoplasm and especially of nucleus proved more reliable criteria of megaloblastic changes than did cell size, especially in marrow preparation from patients with associated iron deficiency.

In order to determine the range of variation of the bone marrow in normal pregnancy and puerperium, studies of the bone marrow were made in 30 women in each of the three trimesters of pregnancy; 10 studies were performed on each of the first eight postpartum days and 30 studies were made six weeks post partum. The pregnancies and puerperia of these women were normal in every respect and hematological studies of the blood performed at the same time as the bone marrow aspirations were normal. The bone marrow of simple iron deficiency anemia was studied in a group of pregnant and puerperal

women and in a group of nonpregnant women. Marrow studies were also performed in a group of pregnant women with normochromic normocytic anemia without megaloblasts in the bone marrow. The results of these studies are being reported separately. For the purposes of this paper it is sufficient to state that megaloblasts, intermediate megaloblasts, and macrogranulocytes were not found in the bone marrow of the group of patients just described.

Consequently, the presence of megaloblasts, intermediate megaloblasts, and/or macrogranulocytes is believed to be diagnostic of megaloblastic anemia.

Response to Therapy

From a study of the plotted response of these patients to therapy it is apparent that criteria of response which are accepted for other megaloblastic anemias are not applicable to some of the megaloblastic anemias of pregnancy and the puerperium. Our studies demonstrate a number of reasons for this statement.

1. There are marked individual blood and especially plasma volume fluctuations throughout pregnancy and early in the puerperium.[1, 2] These fluctuations may be amplified during early response to specific therapy as demonstrated in Figs. 1, 2, 7, and 10.

2. For some unknown reason the hematological response to therapy, especially ante partum, is often slower than in other megaloblastic anemias.

3. In other megaloblastic anemias it is generally known that a satisfactory reticulocyte response is not always followed by a satisfactory red-cell increase, and that in other instances an unsatisfactory reticulocyte response may be followed by a satisfactory rise of red cells. These observations are even more applicable to cases of megaloblastic anemia of pregnancy and the puerperium.

4. An associated iron deficiency was present initially in 10 of our patients and became apparent during response to therapy in several others. In some instances this iron deficiency seemed to impair the red-cell response to specific antimegaloblastic antianemia therapy. A similar experience had been recorded by others.

5. Although the reticulocyte and particularly the red-cell response were studied in every patient and in some instances showed decisive results, serial bone marrow findings presented the only single reliable criterion of response to specific therapy.

TABLE I. RESPONSE OF BONE MARROW TO THERAPY IN 19 CASES OF MEGALOBLASTIC ANEMIA

THERAPY	RESPONSE		
	COMPLETE	PARTIAL	NEGATIVE
Oral vitamin B_{12}	1	0	2
I.M. vitamin B_{12}	2	1	4
I.M. folic acid, initially	1	0	0
After vitamin B_{12} failure	3	1	0
After response to Leucovorin or vitamin B_{12}	0	0	3
I.M. Leucovorin	5	1	0
I.V. iron initially	0	0	1
In hypochromic anemia following improvement of megaloblastosis	6	0	1
Spontaneous remission post partum	3	0	0

The response of the bone marrow to the various therapeutic agents is depicted in Figs. 1-17 and in Table I. One patient responded and 2 failed to respond to oral vitamin B_{12}. Three patients responded and 4 failed to

respond to parenterally administered vitamin B_{12}. One patient responded initially to folic acid and 4 responded to this substance after failing to respond to vitamin B_{12}. No patient who received folic acid in relapse failed to respond. Six patients responded to treatment with folinic acid, although only one responded partially. Three patients developed spontaneous remission post partum. Intravenous iron was administered initially in one patient without improvement; secondary response to intravenous iron was obtained on 6 occasions after successful specific treatment of the marrow megaloblastosis.

Comment

Bone Marrow Findings.—

Although it is generally accepted that the bone marrow of pernicious anemia in full relapse is characterized by the presence of megaloblasts, there are morphological points of disagreement which are pertinent to other megaloblastic anemias, including that associated with pregnancy.[4-10] There is no full agreement on the exact cellular derivation of the promegaloblasts. The undifferentiated primitive reticulum cell, the less immature but still multipotential derivatives of this cell, and the earliest differentiated nucleated red cell (proerythroblast or erythrogone) have all been stated to be the immediate precursors of the promegaloblast. Most recent reports have disagreed with the view[11] that megaloblasts are normal primitive erythroblasts and that the marrow shows an arrest of maturation at the megaloblastic level in pernicious anemia in relapse. Another group regards the megaloblast as belonging to a pathological strain of erythrocytes with no transitional forms intermediate between typical normoblasts and typical megaloblasts.[5, 6] This concept would deny the existence of relative deficiencies causing partial megaloblastic transitions and consequently would appear contrary to the established observations in deficiency diseases.

Our findings support the hypothesis that megaloblasts represent an abnormality of erythroblastic division, growth, and maturation due to deficiency or improper utilization of one or more hemopoietic factors. According to this concept all degrees of deviation from typical normoblastic to the classical megaloblastic erythropoiesis may be observed at all levels of maturation, depending upon the degree of deficiency and, to some extent, upon the time factors involved. Some authors require slight morphological changes from typical normoblasts and others require more marked changes to indicate early megaloblastic transformation.

The megaloblastic anemia of pregnancy rarely develops before the second trimester and usually is first detected in the third trimester or post partum. Most often delivery is followed by spontaneous remission of the anemia. Our bone marrow studies from untreated cases showed great variation in the degree of deviation toward the typical megaloblast.

Several studies of the bone marrow in normal pregnancy have been reported in the literature. Some of these reports may be criticized because of inclusion of bone marrow from anemic patients, failure to record red-cell values, the small number of marrow studies performed, the use of unacceptable standards of nonpregnant normal values for comparison, and/or confusion of classification and terminology of the cell types involved. Daniachij[12] and also Russo[13] reported

the presence of small numbers of megaloblasts in the bone marrow in normal pregnancy. No other author has confirmed these findings. Several authors[14, 15, 16] found no essential difference between the bone marrow of normal pregnancy and the nonpregnant normal. Some[17-20] found evidence of increased erythropoiesis during the latter months of pregnancy, whereas Wolff and Limarzi noted no increase of erythropoiesis in normal pregnancy.

Most authors observed increased granulopoiesis during the latter part of pregnancy.[17-21] Several observed large granulocytes but Callender found the variations of granulopoiesis to be the same as in her nonpregnant controls. Wolff and Limarzi noted megakaryocytic hyperplasia. Post partum, Markoff found the marrow to be identical with that of the nonpregnant normal, whereas the granulocytic hyperplasia did not return to nonpregnant normal for three months in the studies of Wolff and Limarzi.

Because of these controversial results it seemed desirable to study the bone marrow of nonpregnant women of the same age period, of a sizable number of normal pregnant and puerperal women, and also the bone marrow in various forms of nonmegaloblastic anemia occurring in both the pregnant and the nonpregnant state. From these studies it was concluded that megaloblastic anemia may be diagnosed when megaloblasts, intermediate megaloblasts, and/or macrogranulocytes are found in the bone marrow.

In general, but not always, the degree of megaloblastosis paralleled the severity of anemia. Only the severe cases showed a degree of megaloblastosis approaching that seen in Addisonian pernicious anemia in full relapse. As a result of hematological screening, anemia is detected in most of our patients before it becomes severe. Demonstration of intermediate megaloblasts and/or macrogranulocytes in the bone marrow of these patients permits early recognition of the megaloblastic nature of the anemia. Similar findings have been observed in other megaloblastic anemias.[8, 22-26]

During the course of this study several mild to moderate normochromic normocytic anemias were observed in which there were significant numbers of large proerythroblasts in the bone marrow. These cells were too primitive to be differentiated into premegaloblasts, intermediate promegaloblasts, or macropronormoblasts. Unless more mature cells, exhibiting definite megaloblastic deviation, were present, these patients were omitted from this study.

Often the response to effective therapy was slower and larger dosage of hemopoietic factor was required than is usual in comparable relapse in other megaloblastic anemias. Bone marrow studies performed during this slow response showed incomplete reversion to normoblastic erythropoiesis, characterized by progressive transition through intermediate cells until eventually normoblastosis was restored. Comparable stages of transition from normoblasts to megaloblasts were observed before treatment in the less severe anemias.

These studies would indicate that the deficiency causing megaloblastic deviation is often relative and that transition to or from typical megaloblasts

is gradual and progressive. This transition probably occurs through successive mitotic divisions of the less mature cells, although mitoses were also seen in late polychomatophilic megaloblasts and intermediate megaloblasts.

The presence of macrogranulocytosis in the blood and bone marrow of patients with all varieties of megaloblastic anemia is well established.[5, 7]

It is interesting to speculate that the automatic termination of pregnancy often limits the extent of development of megaloblastic anemia and that the early megaloblastic changes occur much more frequently than is commonly thought. Inasmuch as the hemopoietic factors deficient in megaloblastic anemia are also utilized by nonhemopoietic cells as growth factors for the body tissues generally, the existence of an apparently mild deficiency of these factors may have important significance.

Foy and his co-workers[27, 28] found that macrogranulocytosis, in particular the giant stab cells, were as typically diagnostic of nutritional megaloblastic anemia as were true megaloblasts. They found some cases with red cell counts of 1 to 2 million in which the bone marrow contained no megaloblasts, but did contain giant stab cells; these patients responded as specifically to treatment as those in whom megaloblasts were present. On the basis of these findings they hypothesized a white-cell maturation factor, the absence of which is responsible for the production of giant stab cells.

Although macrometamyelocytes or giant stab cells exhibited the most spectacular alteration in the white cells, all stages of maturation of granulopoiesis were affected in the bone marrow of our patients. Similar macrogranulocytosis was not observed in the control marrow studies which were discussed earlier. Consequently, we would agree that the presence of macrogranulocytes is of diagnostic significance.

Spontaneous remission, which often is slow and partial, but which may occur rapidly, usually occurs during the puerperium, although megaloblastic anemia developing during the puerperium has been described.

Therapy.—

Following the discovery of Minot and Murphy in 1926 that Addisonian pernicious anemia responded to the feeding of whole liver, it soon became apparent that other megaloblastic anemias responded similarly to the feeding of whole liver, to liver extract, or to the parenteral administration of liver extract. Improvement of megaloblastic anemia of pregnancy after liver treatment was rapidly reported by a number of authors.[29, 36] The early liver extracts were crude preparations and, with whole liver, may have contained significant amounts of folic acid and/or other unknown factors in addition to the antipernicious anemia factor. Beginning in 1931, Wills and her co-workers showed that nutritional macrocytic anemia in humans in India, and in monkeys on comparable diet, would respond to an autolyzed yeast preparation (Marmite). Later reports indicated response also to injections of a crude liver extract (Campolon),[36, 39] but not as well as to refined liver extract (Anahaemin).[37, 40, 42, 43, 114] It must be remembered that these tropical nutritional megaloblastic anemias occur in men and nonpregnant women as well as

pregnant women and hence are believed by many to differ from megaloblastic anemia of pregnancy and the puerperium occurring in temperate climates. Furthermore, the tropical and subtropical cases are frequently complicated by other nutritional deficiencies, malaria, intestinal infestations with worms, or by amebiasis. The Macedonian cases exhibited a hemolytic component and had a high incidence of malaria[44, 45]; the anemia responded to massive doses of Marmite and also to injections of both crude and refined liver extract. Likewise, megaloblastic anemia of pregnancy in temperate climates was found to respond variably to autolyzed yeast.[46, 50]

With the increasing refinement of liver extracts, reports of failure, slow or incomplete and atypical responses of megaloblastic anemia of pregnancy and the puerperium in temperate climates appeared in the literature.[34, 46, 48, 50-60, 62, 63, 104, 105, 111, 112] Some cases of this group of anemias in temperate climates have responded satisfactorily to parenteral administration of refined liver extract. An occasional patient has responded to very large amounts of parenteral refined liver extract after small amounts have failed.[29, 34-36, 63-65, 110] In some instances crude liver extracts parenterally have seemed more effectual than refined liver extracts.[50, 54] In other instances the anemia has responded to oral administration of whole liver,[46, 48, 52, 54] crude liver extract,[50, 58] proteolyzed liver,[66-69] yeast extract or Marmite,[41, 46, 54, 58] and preparations of hog's stomach after failing to respond to parenteral liver extract therapy.

In temperate climates megaloblastic anemia of pregnancy and the puerperium has generally failed to respond to vitamin B_{12},[54, 60, 62, 69, 70-72] even in very large doses.

Many cases, both in tropical and in temperate climates, have responded satisfactorily to folic acid[3, 38, 39, 54, 55, 59-62, 68-80, 106-109, 113] in many instances, after having failed to respond to refined liver extract or to vitamin B_{12}. In the tropics and subtropics, however, several authors have reported satisfactory response to vitamin B_{12},[62, 65, 81-84] whereas in temperate climates only one patient from Holland has been reported to respond to vitamin B_{12}.[84]

As is to be expected from the results with folic acid, *Leuconostoc citrovorum* factor has been found effectual in a few cases which have been treated with this substance.[69, 85]

In the tropics and subtropics an occasional patient has responded to vitamin B_{12} or refined liver extract and not to folic acid.[61] In temperate climates some patients have failed to respond to folic acid as well as to vitamin B_{12} but no patient has been reported to respond to vitamin B_{12} after failure with folic acid.

Megaloblastic anemia is often complicated by the presence of iron deficiency which may be apparent before the initiation of therapy, or may become apparent only as response to therapy produces new cells requiring iron. The usual story is the presence of an apparent iron-deficiency anemia which masks the underlying megaloblastic anemia. Only after the patient has failed to respond to iron is megaloblastic anemia detected. After initial response of

the megaloblastic anemia to specific therapy, many patients will require iron therapy to complete the response[80] and to restore the hemoglobin to physiological levels. An occasional instance of combined megaloblastic and iron-deficiency anemia has been reported which responded to treatment of the megaloblastic anemia only after correction of the iron deficiency. Our data would indicate that a very mild megaloblastic component, which is occasionally present in an iron-deficiency anemia associated with pregnancy, may not be sufficient to interfere with the patient's response to iron.

Etiology.—

Many authors have stated that the megaloblastic anemia of pregnancy and the puerperium in tropical and subtropical climates differs from the so-called pernicious anemia of pregnancy in temperate climates.[96] In the tropics and subtropics this anemia is associated almost invariably with nutritional deficiency[41, 96] and often with complicating malarial, syphilitic, and parasitic infection. A similar disease occurs in males and nonpregnant females and cases have been reported which respond to small amounts of refined liver extract or to vitamin B_{12}. In contrast, it is stated that cases of megaloblastic anemia of pregnancy and the puerperium in temperate climates often are not associated with nutritional deficiency or complicating infection, have no counterpart in males and nonpregnant females, and rarely respond to refined liver extract and never to vitamin B_{12}.

It is our opinion that this differentiation is not entirely valid. Many similarly malnourished pregnant women in India do not develop megaloblastic anemia.[38, 39, 86] A large proportion of our patients and many of those reported by other authors gave a history of inadequate diet and/or significant vomiting. It has been shown that absorption of certain food factors may be decreased in pregnancy in the absence of the sprue syndrome. The incidence and types of malnutrition differ in the tropical, subtropical, and temperate countries, in large part as determined by dietary custom and the amount of dire poverty. Consequently, the specific dietary deficiencies probably differ. It has been shown that meat and vegetable products, with the exception of liver, lose much of their folic acid content during the process of cooking and canning.[87, 91] A similar loss is well known in the case of vitamin C. It has been estimated that the pregnant woman requires a daily supplement of 2 to 5 mg. of folic acid.[3] Our studies would indicate that it is likely that nutritional deficiency of vitamin B_{12}, folic acid, and/or possibly a third factor (Wills factor?) is the cause of the majority of the megaloblastic anemias of pregnancy and the puerperium in temperate climates. In addition to inadequate intake and the added burden of fetal requirements, this nutritional deficiency may also be conditioned in some instances by alterations in intestinal flora, which alternately compete with the body for the factors just mentioned, or synthesize them, and by impaired intestinal absorption of these factors. Deficient gastric intrinsic factor would not seem important in most instances. Nor is there sufficient evidence to support the hypothesis that an endocrine abnormality causes these anemias.

Accessory deficiency of ascorbic acid has been shown to be important in some cases of megaloblastic anemia of infancy and in folic acid-deficient nutritional megaloblastic anemia of monkeys.[92, 96] It is not known whether a comparable analogy exists in the cases occurring in pregnancy and the puerperium. This seems unlikely in view of the high intake of supplementary vitamin C in some of our patients. In this connection it is of more than passing interest that since June of 1953 daily vitamin supplements containing 3.0 mg. of folic acid and 4.5 mg. of vitamin B_{12} have been prescribed to all pregnant women attending the antenatal clinic of the Royal Victoria Hospital, and that not one case of megaloblastic anemia of pregnancy or the puerperium has been detected during this period.

The variability of response to treatment with both the same and different substances has caused students of the disease to conclude that megaloblastic anemia of pregnancy and the puerperium represents a group of conditions which are not etiologically homogenous, but which exhibit a common resultant, the development of anemia due to megaloblastic bone marrow. Aside from the amino acid building blocks, folic acid, vitamin B_{12}, possibly ascorbic acid and the so-called Wills factor, other unknown accessory factors are probably required for the synthesis of erythroblastic nucleoprotein. There are considerable interrelation and interdependence of these factors in their action and it seems probable that a functional deficiency of any one or combination of them may eventuate in a common resultant, namely, megaloblastic anemia.[37, 39, 41, 42, 50, 97-99]

When Vitamin B_{12} is administered to the normal person or to patients with Addisonian pernicious anemia, urinary excretion of folic acid is sharply increased.

It is possible that, in the presence of a partial deficiency of folic acid in the megaloblastic anemias occurring in temperate climates, vitamin B_{12}, by mass action, may mobilize the folic acid remaining in the body tissues and in this way cause a partial or complete remission of the disease. When the tissues have been depleted so that no folic acid is available to the mobilizing influence of vitamin B_{12}, then therapy with this agent may fail to produce remission of the disease. In other instances it is conceivable that a true deficiency of vitamin B_{12} is the responsible factor. The latter deficiency probably occurs uncommonly in temperate climates and somewhat more frequently in tropical and subtropical climates; in some instances, especially in the latter areas, the deficiency may be due to a combined deficiency of vitamin B_{12} and of folic acid. There is certainly need for careful dietary surveys and quantitative vitamin B_{12} and folic acid balance studies. Knott and Suarez[100] in Puerto Rico found a slight decrease of urinary folic acid excretion in normal pregnant women during the last trimester, and a further decrease during the first week post partum.

The satisfactory remission obtained by Foy and associates[101, 102] by penicillin and Aureomycin in nutritional megaloblastic anemia in pregnancy in Kenya is thought to be due to the effect of penicillin in altering the intestinal flora. There still remains the possibility of a toxic factor elaborated by abnormal intestinal flora in these cases, analogous to blind intestinal loop anemia.

In all areas an occasional patient has been found with this disease who had not responded to either vitamin B_{12} or to folic acid, which would suggest that there is a third factor (Wills factor?) which may be deficient in the occasional patient.

If one accepts the nutritional deficiency theory of etiology, increased incidence of megaloblastic anemia in multiple pregnancies may be due to the increased nutritional needs of twin fetuses as compared with a single fetus.

There are other considerations which may affect the response to specific therapy. It is well established that the anemia is more refractory to therapy ante partum, than it is post partum. Some patients, who have proved refractory to refined liver extract ante partum have seemed to respond to this therapy post partum.

In assessing postpartum response to therapy the possibility of spontaneous remission must be considered and often makes such assessment extremely difficult. Just as active infection may increase the specific therapeutic requirements in Addisonian pernicious anemia, so it is possible that complicating infection, toxemia, hemorrhage, and the presence of other deficiencies may retard or inhibit the therapeutic response in megaloblastic anemia of pregnancy and the puerperium. The development of the disease state in apparently well-nourished women in temperate climates and the poor response or failure of response to therapy ante partum, as well as the occurrence of spontaneous postpartum remission, have led some to suggest that the disease is of endocrine origin. The few efforts to find a responsible endocrine abnormality have yielded conflicting results.[62] Complicating infection has been more prominent in some series than in others. At most, it appears to be of secondary rather than of primary etiological importance.

In 1932 Strauss and Castle[103] demonstrated that in some cases of megaloblastic anemia of pregnancy gastric intrinsic factor may be temporarily depressed. This group of megaloblastic anemias of pregnancy and the puerperium might be expected to respond to parenteral administration of refined liver extract or vitamin B_{12}. One of their patients and two additional ones, as discussed in a later article[50] exhibited a basic deficiency, which was not intrinsic or extrinsic factor, and which was contained in crude liver extract. This deficient factor may have been folic acid or the so-called Wills factor. These experiments foreshadowed the recognition that megaloblastic anemia of pregnancy and the puerperium may develop in temperate climates as the result of nutritional deficiency of at least two different accessory factors.

Summary and Conclusions

1. Clinical and hematological studies are reported upon nineteen cases of megaloblastic anemia of pregnancy and the puerperium observed in a three-year period at the Royal Victoria Montreal Maternity Hospital.

2. The anemia appears to have been caused by dietary nutritional deficiency in most instances.

3. There were no pathognomonic clinical symptoms or signs. Only occasionally could the diagnosis be established from the various hematological findings in the blood and only then by the presence of megaloblasts, intermediate megaloblasts, and/or macrogranulocytes in the blood smears.

4. In most instances cytological studies of the bone marrow were the only reliable method of establishing the diagnosis.

5. The bone marrow findings in these patients were compared with the marrow findings in a large number of normal pregnant and puerperal women, with iron deficiency and posthemorrhagic anemias occurring in both pregnant and nonpregnant women, and with a large group of miscellaneous anemias associated with pregnancy. As a result of these studies it may be stated that in the pregnant or puerperal woman the presence of megaloblasts, intermediate megaloblasts, and/or macrogranulocytes in the bone marrow permits the diagnosis of megaloblastic anemia. The degree of megaloblastosis reflects the degree and duration of deficiency of specific hemopoietic factors existing in the body tissues.

Mild deficiency with transitional forms only (intermediate megaloblasts) and/or a number of giant stab cells in the marrow occurred much more frequently than the classical fully developed megaloblastic anemia. Normoblastosis, variable in amount, was always present in these marrows.

6. Coexisting iron deficiency was either present or developed during specific response to the treatment of the megaloblastic anemia in many cases.

7. The findings suggested the presence of a hemolytic component in three patients.

8. The bone marrow findings support the concept that the megaloblast is an abnormal variant of the normoblast, which may undergo all degrees of transition, depending upon the severity of the responsible deficiency or deficiencies.

9. In contrast to the reports from other centers in temperate climates, one patient responded to oral vitamin B_{12} and three responded to parenteral vitamin B_{12} administration. Four cases in which vitamin B_{12} therapy failed subsequently responded to folic acid. Six patients responded to folinic acid. There were no folic or folinic acid failures. Spontaneous remission occurred in three instances.

10. Serial bone marrow study was the most accurate single measure of the response to therapy.

11. Minimal effectual dosage was greater and response to therapy was slower in pregnancy than is usually the case in Addisonian pernicious anemia.

12. In temperate climates megaloblastic anemia associated with pregnancy and the puerperium may result from a deficiency of folic acid, vitamin B_{12} and/or possibly an unknown factor. The best and most consistent response to therapy was obtained with folic acid and folinic acid.

13. These studies suggest that mild deficiency of one or more of these substances occurs more frequently than is commonly believed.

14. The disappearance of this anemia from the wards and clinics of our hospital since June, 1953, when the antepartum daily supplement of 4.5 μg. of vitamin B_{12} and 3.0 mg. of folic acid was initiated may have more than passing significance.

References

1. Tysoe, F. W., and Lowenstein, L.: Am. J. Obst. & Gynec. **60**: 1187, 1950.
2. Lowenstein, L., Pick, C. A., and Philpott, N. W.: Am. J. Obst. & Gynec. **60**: 1206, 1950.
3. Spies, T. D.: Surg., Gynec. & Obst. **89**: 76, 1949.
4. Jones, O. P.: Anat. Rec. (supp.) **58**: 23, 1934.
5. Jones, O. P.: In Downey, H., editor: Handbook of Hematology, New York, 1938, Paul B. Hoeber, Inc., vol. 3, p. 2043.
6. Jones, O. P.: Arch. Path. **33**: 752, 1943.
7. Dameshek, W., and Valentine, E. H.: Arch. Path. **23**: 159, 1937.
8. Dacie, J. V., and White, J. C.: J. Clin. Path. **2**: 1, 1949.
9. Downey, H.: J. Lab. & Clin. Med. **39**: 837, 1952.
10. Sundberg, R. D., Schaar, F., and May, C. D.: Blood **7**: 1143, 1952.
11. Doan, C. A., Cunningham, R. S., and Sabin, F. R.: Contrib. Embryol. **16**: 163, 1925.
12. Daniachij, M. A.: Zentralbl. Gynäk. **60**: 1220, 1936.
13. Russo, F.: Ann. ostet. e ginec. **59**: 1169, 1937.
14. Pitts, H. H., and Packham, E. A.: Arch. Int. Med. **64**: 471, 1939.
15. Forssel, J.: Acta med. scandinav. (supp.) **101**: 62, 1939.
16. Callender, S. T.: J. Path. & Bact. **58**: 586, 1946.
17. Markoff, N.: Ztschr. Geburtsh. u. Gynäk. **119**: 13, 1939.
18. Pignoli, R.: Haematologica **24**: 1103, 1942.
19. Leitner, S. J.: Bone Marrow Biopsy; Hematology in the Light of Sternal Puncture, ed. 2, New York, 1949, Grune & Stratton, p. 394.
20. Hanson, R.: Ztschr. Geburtsh. u. Gynäk. **116**: 398, 1937.
21. Wolff, J. R., and Limarzi, L. R.: J. A. M. A. **128**: 482, 1945.
22. Lambin, P., and de Weerdt, W.: Rev. belge sc. méd. **10**: 282, 1938.
23. Jones, O. P.: Anat. Rec. **94**: 473, 1946.
24. Zuelzer, W. W., Newhall, A., and Hutaff, L.: J. Lab. & Clin. Med. **32**: 1217, 1947.
25. Davidson, L. S. P., Davis, L. J., and Innes, J.: Quart. J. Med. **11**: 19, 1942.
26. Schartum-Hansen, H.: Acta med. scandinav. (supp.) **218**: 7, 1948.
27. Foy, H., Khondi, A., and Hargreaves, A.: Lancet **2**: 1172, 1950.
28. Foy, H., and Khondi, A.: Lancet **2**: 360, 1939.
29. Brault, P. L.: Bull. Soc. obst. et gynéc. **17**: 619, 1928.
30. Davidson, L., and Laennec, T.: Bull. Soc. obst. et gynéc. **17**: 213, 1928.
31. Beckman, M.: Zentralbl. Gynäk. **52**: 2553, 1928.
32. Peterson, R., Field, H., Jr., and Morgan, H. S.: J. A. M. A. **94**: 839, 1930.
33. Dyke, S. C.: Proc. Roy. Soc. Med. **24**: 935, 1931.
34. Stevenson, E. M. K.: Tr. Edinburgh Obst. Soc. **58**: 81, 1938.
35. Segerdahl, E.: Acta med. scandinav. **108**: 483, 1941.
36. Mudaliar, A. L., and Menon, M. K. K.: J. Obst. & Gynaec. Brit. Emp. **49**: 284, 1942.
37. Wills, L., and Evans, B. D. F.: Lancet **2**: 416, 1938.
38. Napier, L. E., Das Gupta, C. R., Chandhuri, R. N., Sen, G. N., Rai Chandhuri, M. N., Sen Gupta, P. C., and Majunder, D. N.: Indian M. Gaz. **73**: 385, 1938.
39. Kothari, B. V., and Bhende, Y. M.: Indian J. M. Res. **40**: 387, 1952.
40. Wills, L.: Brit. M. J. **1**: 1059, 1931.
41. Wills, L.: Indian J. M. Res. **21**: 669, 1934.
42. Wills, L., Clutterbuck, P. W., and Evans, B. D. F.: Biochem. J. **31**: 2136, 1937.
43. Napier, L. E.: Indian M. Gaz. **74**: 1, 9, 1939.
44. Fairley, N. H., Brombield, R. J., Foy, H., and Khondi, A.: Tr. Roy. Soc. Trop. Med. & Hyg. **32**: 132, 1938.
45. Foy, H., and Khondi, A.: Lancet **2**: 360, 1939.
46. Ungley, C. C.: Lancet **1**: 925, 1938.
47. Doan, C. A.: In Downey, H., editor: Handbook of Hematology, New York, 1938, Paul B. Hoeber, Inc., vol. 3, p. 1843.
48. Miller, H. G., and Studdert, T. C.: Lancet **2**: 332, 1942.
49. Strauss, M. B., and Castle, W. B.: Am. J. M. Sc. **185**: 539, 1933.
50. Watson, J., and Castle, W. B.: Am. J. M. Sc. **211**: 513, 1946.
51. Föderl, V.: Wein. Klin. Wchnschr. **51**: 168, 1938.
52. Fullerton, H. W.: Brit. M. J. **1**: 158, 1943.
53. Callender, S. T. E.: Quart. J. Med. **13**: 75, 1944.

54. Thompson, R. B., and Ungley, C. C.: Quart. J. Med. **20**: 187, 1951.
55. Goldenberg, H., and Wyatt, J. P.: Canad. M. A. J. **63**: 289, 1950.
56. Ginsberg, V., Watson, J., and Lichtman, H.: J. Lab. & Clin. Med. **36**: 238, 1950.
57. Dockeray, G. C.: Irish J. M. Sc., p. 126, March, 1938.
58. Nielson, O. P.: Acta med. scandinav. **108**: 421, 1941.
59. Davidson, L. S. P., Girdwood, A. H., and Clark, J. A.: Brit. M. J. **1**: 519, 1948.
60. Bethell, F. H., Myers, M. C., and Neleigh, M. B.: J. Lab. & Clin. Med. **33**: 1477, 1948.
61. Das Gupta, C. R., Chatterjea, J. B., and Mathen, K. K.: Indian J. M. Res. **37**: 455, 1949.
62. Day, L. A., Hall, B. E., and Pease, G. L.: Proc. Staff Meet., Mayo Clin. **24**: 149, 1949.
63. Bethell, F. H.: J. Am. Dietet. A. **26**: 89, 1950.
64. Abramson, L.: Acta med. Scandinav. **96**: 319, 1938.
65. Lescher, F. G.: Lancet **2**: 148, 1942.
66. Davis, L. J., Davidson, L. S. P., Riding, D., and Shaw, G. E.: Brit. M. J. **1**: 655, 1943.
67. Davis, L. J., and Davidson, L. S. P.: Quart. J. Med. **13**: 53, 1944.
68. Davidson, L. S. P.: Blood **3**: 107, 1948.
69. Clark, J. R.: Edinburgh M. J. **59**: 274, 1952.
70. Ungley, C. C., and Thompson, R. B.: Brit. M. J. **1**: 919, 1950.
71. Furman, R. H., Daniels, W. B., Jr., Hefner, L. L., Jones, E., and Darby, W. J.: Am. Pract. **1**: 146, 1950.
72. Ginsberg, V., Watson, J., and Lichtman, H. J.: J. Lab. & Clin. Med. **36**: 239, 1950.
73. Benjamin-Allan, A.: Indian J. M. Sc. **2**: 199, 1948.
74. Andre, R.: Bull. et Mém. Soc. méd. Hôp. Paris **65**: 207, 1949.
75. Eisenberg, S. E.: Yale J. Biol. & Med. **21**: 161, 1948.
76. Israels, M. C. G., and Da Cunha, F. A. L.: Lancet **2**: 214, 1952.
77. Das Gupta, C. R., and Chatterjea, J. B.: Blood **6**: 631, 1951.
78. Clarke, J. P., and Essig, L. L.: Am. J. Obst. & Gynec. **67**: 367, 1954.
79. Houpst, G.: Nederl. tijdschr. v. geneesk. **92**: 557, 1948; J. A. M. A. **137**: 1634, 1948.
80. Allan, W. B.: Indian J. M. Sc. **2**: 199, 1948.
81. Patel, J. C., and Koch, B. R.: Brit. M. J. **1**: 924, 1950.
82. Chandhuri, S.: Brit. M. J. **2**: 825, 1951.
83. Manson-Bahr, P. E. C.: J. Trop. Med. & Hyg. **54**: 89, 1951.
84. Nieweg, H. O.: Lancet **2**: 491, 1952.
85. Davidson, L. S. P., and Girdwood, R. H.: Lancet **2**: 1193, 1951.
86. Bhende, Y. M.: Indian J. M. Sc. **3**: 211, 1949.
87. Cheldelin, V. H., Woods, A. M., and Williams, R. J.: J. Nutrition **26**: 477, 1943.
88. Ives, M., Pollard, A. E., Eveljem, C. A., and Strong, F. M.: J. Nutrition **31**: 347, 1946.
89. Angulo, J. J., and Spies, T. D.: Am. J. Trop. Med. **27**: 317, 1947.
90. Fager, E. E. G., Olson, O. E., Burris, R. A., and Eveljem, C. A.: Food Res. **1**: 14, 1949.
91. Hanning, F., and Mittis, M. L.: J. Am. Dietet. A. **25**: 226, 1949.
92. May, C. D., Sundberg, R. D., Scharr, F., Lowe, C. U., and Salmon, R. J.: Am. J. Dis. Child. **82**: 282, 1951.
93. May, C. D., Nelson, E. N., and Salmon, R. J.: J. Lab. & Clin. Med. **34**: 1724, 1949.
94. May, C. D., Nelson, E. N., Salmon, R. J., Lowe, C. U., Leinke, R. I., and Sundberg, R. D.: Bull. Univ. Minnesota Hosp. Staff **21**: 208, 1950.
95. May, C. D., Sundberg, R. D., and Schaar, F.: J. Lab. & Clin. Med. **36**: 963, 1950.
96. Wills, L., and Mehta, M. M.: Indian J. M. Res. **17**: 777, 1929-1930.
97. Bethell, F. H.: J. A. M. A. **107**: 564, 1936.
98. Bethell, F. H., Blecha, E., and Van Sant, J. H.: J. Am. Dietet. A. **19**: 165, 1943.
99. Wills, L.: Blood **3**: 36, 1948.
100. Knott, E. M., and Suarez, R. M.: Federation Proc. **8**: 387, 1949.
101. Foy, H., and Khondi, A.: Brit. M. J. **1**: 380, 1951.
102. Foy, H., Khondi, A., and Hargreaves, A.: Brit. M. J. **1**: 852, 1952.
103. Strauss, M. B., and Castle, W. B.: New England J. Med. **207**: 55, 1932.
104. Ritter, J. A., and Crocker, W. J.: Am. J. Obst. & Gynec. **38**: 239, 1939.
105. Davidson, L. S. P., Davis, L. J., and Innes. J.: Brit. M. J. **2**: 31, 1942.
106. Davidson, L. S. P., and Girdwood, R. H.: Lancet **2**: 373, 1946.
107. Eisenberg, S.: Yale J. Biol. & Med. **21**: 161, 1948.
108. Spies, T. D.: J. A. M. A. **130**: 474, 1946.
109. Goodall, J. W. D., Goodall, H. T., and Banarjee, D.: Lancet **1**: 20, 1948.
110. Trowell, H. C.: Lancet **1**: 43, 1943.
111. Elliott, G. A.: J. Obst. & Gynaec. Brit. Emp. **49**: 284, 1942.
112. Davidson, L. S. P., Davis, L. J., and Innes, J.: Edinburgh M. J. **50**: 431, 1943.
113. Ungley, C.: J. Pharm. & Pharmacol. **2**: 540, 1950.
114. Kothari, B. V., and Bhende, Y. M.: Indian J. M. Res. **40**: 387, 1952.

THE TREATMENT OF UTERINE INERTIA WITH DILUTE INTRAVENOUS PITUITRIN*†

DAVID B. MOORE, M.D., AND D. ANTHONY D'ESOPO, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, the Sloane Hospital for Women, and Vanderbilt Clinic, Presbyterian Hospital)

THE administration of Pituitrin by the intravenous route seems to have been first reported by Page[1] in 1943 as capable of producing the most physiologic response in severe primary uterine inertia. Theobald and his co-workers[2] reported twenty cases treated in this way in 1948. Hellman[3, 4] in the next two years published the most complete material on this subject and receives credit for having established the intravenous method of administering Pituitrin as a reliable procedure with definite advantages over the intramuscular route. Stone[5] in 1950 reported on the use of Pituitrin infusions at Bellevue Hospital. Besides the advantage of greater controllability of uterine effect in both directions, the intravenous route has been shown by Hellman and his co-workers[4] to exert a more physiologic effect on the uterus. They obtained tokodynamometric evidence of fundal dominance in nearly all the cases treated with intravenous Pituitrin, while the reversal effect was noted more often with intramuscular Pituitrin.

No serious complications have been reported. Nearly all writers report some failures and a variable number of fetal deaths which, in some instances, may be related directly or indirectly to the use of the drug.

The contraindications that these various observers have accepted go back for the most part to the experiences obtained with intramuscular administration of Pituitrin. The woman who has had many repeated pregnancies has been considered a poor candidate for treatment because of the greater susceptibility to uterine rupture. Malpositions have sometimes been included among the contraindications. The contracted pelvis is invariably mentioned as a contraindication although borderline degrees of contraction have not been excluded in most reports. Other contraindications mentioned are the presence of strong uterine contractions without progress in either cervical dilatation or descent, and irregular uterine contractions in patients with "unripe" cervices.

A Clinical Classification of Types of Labor

Before presenting our material we should like to point out that the condition of uterine inertia is in need of better classification. In the course of the study we have had great difficulty in correlating the diagnoses of primary inertia, secondary inertia, and cervical dystocia used almost indiscriminately

*Supported in part by the George F. Baker Trust Gift for Research.
†Presented at a meeting of the New York Obstetrical Society, Feb. 9, 1954.

by the resident and attending staff, with the actual types of labor described in the records. The reason for this confusion as we will show is based on an oversimplification of the existing clinical patterns of atypical labor.

While Reynolds[6] has been able to define uterine inertia in physiologic terms related to the work gradient as evidenced by the tokodynamometer, and Steer[7] expresses it in electrical-wave activity as measured by the electrohysterograph, for the practical clinical approach we must content ourselves, for the time being at least, with purely clinical methods which include observation, palpation of the uterus, rectal and pelvic examinations, and the clock. The subjective reaction of the patient may be important but we are warned that this may lead us astray in both directions. In the final analysis the only reliable clinical criteria that are available to us are some measure of progression in relation to time. The best measure of progress in the first stage is cervical dilatation and, in the second stage, descent of the presenting part.

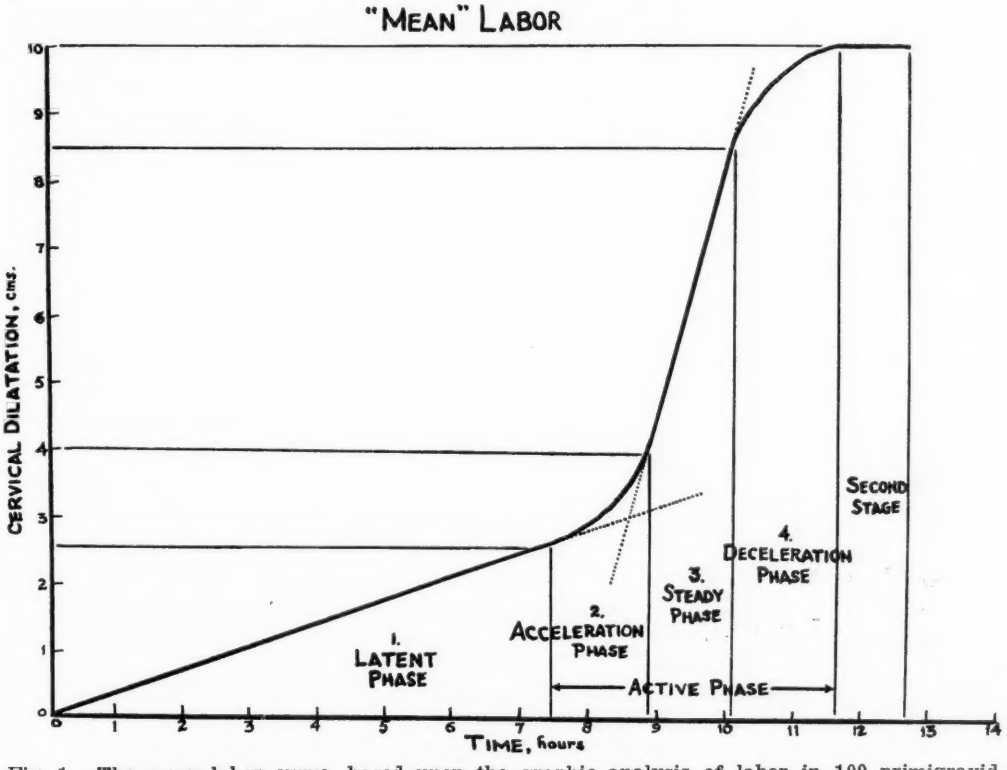


Fig. 1.—The mean labor curve, based upon the graphic analysis of labor in 100 primigravid patients, representing cervical dilatation—time relationship. (After Friedman.[8])

Recently, Friedman[8] has developed what may be called a mathematical tool by which the progression of the first stage of labor may be graphically and very simply expressed. He has related the degree of cervical dilatation to time on xy coordinates and in the normal labor has shown that the curve is of the sigmoid variety as illustrated in Fig. 1. After a latent period of from six to eight hours, when the cervix is undergoing very little dilatational change, there is a short period of acceleration when the slope of the line is slowly changing,

and following this dilatation proceeds at a constant rate of speed up to a point when it is about 4½ fingerbreadths dilated. At this point deceleration takes place until full dilatation is reached. This deceleration phase, like the acceleration phase, is normally short.

Using Friedman's curve, we have divided the first stage of labor into three phases: (1) the latent phase, which includes the actual latent phase and the short acceleration phase; (2) the active phase; (3) the deceleration phase. These three phases, with a normal and an abnormal variant in each phase, may be combined theoretically into eight different patterns of the first stage of labor as illustrated in Table I and Fig. 2.

TABLE I

TYPE	LATENT PHASE	ACTIVE PHASE	DECELERATION PHASE
1	Normal	Normal	Normal
2	Normal	Normal	Arrested
3	Normal	Prolonged	Normal
4	Normal	Prolonged	Arrested
5	Prolonged	Normal	Normal
6	Prolonged	Normal	Arrested
7	Prolonged	Prolonged	Normal
8	Prolonged	Prolonged	Arrested

Among the cases indexed in our files as uterine inertia we were able to find all of the eight types of first-stage labor shown in Table I including on occasion the normal Type 1.

From a practical point of view this representation of labor offers a distinct advantage in permitting a graphic visualization and therefore better understanding of the clinical course of labor. It has an obvious advantage over such terms as primary and secondary inertia which even in the best hands are frequently confused as already stated. Its real value, however, is that the types are based on measurable data.

For a better understanding of the classification, the limits of the terms used are essential. The latent phase, as the term indicates, is the period during which minimal changes take place in the cervical dilatation. As stated, we have included with this the period of acceleration or slow change to the active phase. Calculated in this way the latent phase will usually occupy the time over which the cervix dilates to 1½ to 2 fingerbreadths. It should be made clear, however, that the dividing line between the latent phase and the active phase is not related to a certain point in the dilatation of the cervix but rather to the point where the straight line part of the curve, representing the active phase, begins its upward sweep. The latent phase has been assumed to start at the beginning of uterine contractions which the patient recognizes as regularly recurring pains, provided that they continue intermittently until labor ends. False labor, which cannot be determined except retrospectively, when the pains cease, is excluded. We do not, therefore, accept the notion that false labor merges imperceptibly with true labor. In this respect we agree with Schmitz and co-workers,[9] and disagree with most authorities on the subject of labor. Those who eliminate that part of early labor when there is minimal change in the cervix, should, to be con-

sistent, always begin their computation of the duration of labor at some point after labor pains start, for in nearly all labors the cervix shows no discernible change in its earliest phase. It is understandable that one reason why there has been this discrepancy among obstetricians in calculating the time of the onset of labor stems from their interest in fitting the cases of "prolonged labor" into a more uniform clinical entity. When long periods of latent labor are included in calculating the total duration of labor, it may place cases of relatively normal labor in the prolonged labor group and thus introduce a significant statistical error. To avoid this error, then, it has become necessary to omit unrealistically a varying part of the latent phase of labor. These differences in viewpoint are reconciled by this classification for the pattern of a long latent phase followed by a normal active phase is at once obvious and, in spite of the fact that such a patient may have had contractions over a total period of some twenty-four hours before she is delivered, she fits into an essentially normal category.

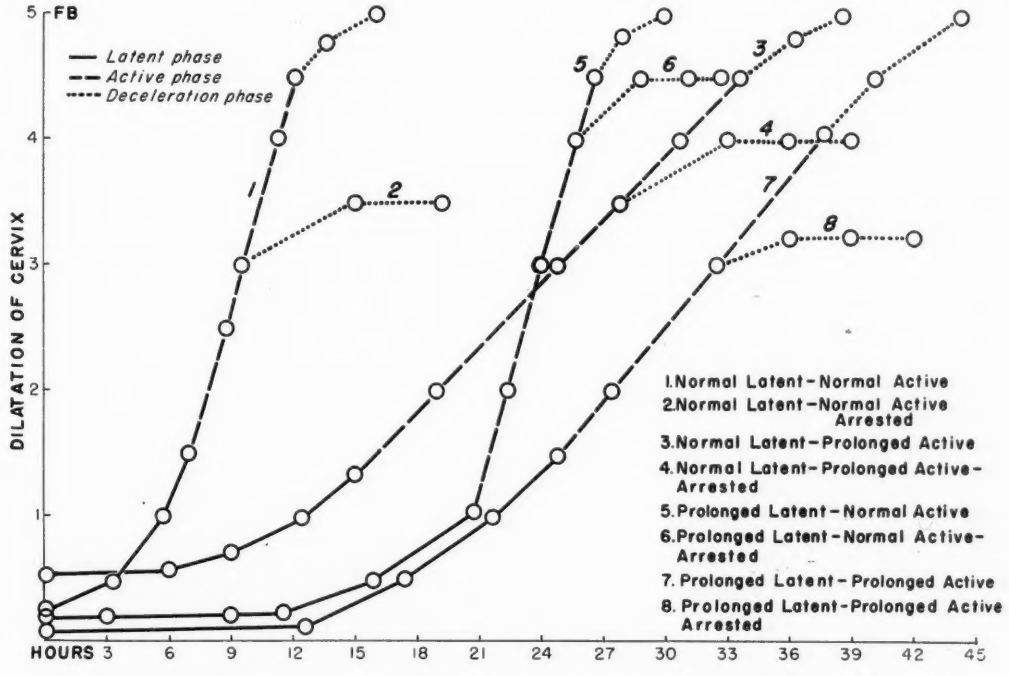


Fig. 2.—Eight theoretical types of first stage labor based upon Friedman's[8] curve.

For the purpose of this classification we have accepted a latent period of eighteen hours or less as normal and over eighteen hours as prolonged. This may require some revision after we have collected this type of graphic data on many more normal cases.

The active phase is less controversial. The cervix dilates at a constant rate of speed so that the plotted points on the graph fall on a straight line. The slope of this line, however, may vary considerably from one that is almost vertical in some multiparas to one that is considerably flattened. A normal slope

in this study was considered to be one which when projected to full dilatation on the graph indicated that the duration of the active phase was eight hours or less. When the slope was flatter, the active phase was considered prolonged. Again the interpretation of these data may require revision in the light of further study.

Finally, the deceleration phase takes on qualitative differences because deceleration may come on prematurely, thus flattening out the original slope of the active phase or become arrested entirely. For the sake of simplicity, we have included both variations of this phase under the term arrested.

Pituitrin infusions have been noted to alter all three of these phases and in this report we will use the terms of this classification to indicate the type of labor that was present when Pituitrin was administered as well as the conversion type which resulted.

Methods and Materials

This study consists of a group of 215 cases of uterine inertia treated intravenously with dilute posterior pituitary extract at the Sloane Hospital from May, 1948, to September, 1953. The product used was Pitocin. During this period of time Pituitrin was given intravenously in an additional 1,400 cases, but these were, for the most part, concerned with the induction of labor and will be reported in a companion publication.

The Pitocin infusion on our service has practically replaced the intramuscular route of administering pituitary extract during the first two stages of labor because of the improved results obtained by virtue of its greater safety, better controllability, and more physiologic response.

The infusion is made up of 10 minims (7 units) of Pitocin in 500 c.c. of 5 per cent glucose in distilled water. We prefer to use this diluent in all cases to avoid the inadvertent administration of saline to a preeclamptic patient. The infusion tubing is filled with solution, cleared of air bubbles, and then closed with a standard Hoffman clamp. A vein is chosen in the forearm, preferably away from the wrist and the antecubital fossa. Venipuncture is made with a No. 19 short-bevel needle and this threaded up the vein as far as possible. The tubing is then attached without any solution flowing and the needle and tubing taped to the forearm. With the use of this technique, the needle usually remains in place even though the patient may move her arm while the infusion is running.

Once the mechanics of attaching the infusion are completed, the drip is initiated at a rate under 10 drops per minute. Six to 8 drops per minute is a fairly good rate since it is fast enough to avoid clotting in the needle. It will be noted that for a variable length of time after the onset of the infusion, usually less than an hour, there will be in most patients an increase in uterine tone between contractions. This has been shown graphically by Hallet and Burgess[10] using internal tokographic techniques. They have also shown that the intracontraction hydrostatic pressure increases temporarily whenever the dosage of Pituitrin is increased. The increased tone can easily be confused with a true tetanic contraction and cause a great deal of unnecessary concern—unnecessary because it will usually disappear spontaneously and will not be associated with any signs of fetal distress.

The ideal rate of infusion must be individualized with each patient. It is our belief that if the rate is to be increased, it should be in not more than 5 drop increments each half hour. This allows time to evaluate each increase and acts

as an added precaution against a tetanic contraction or ruptured uterus. The guide in arriving at an ideal rate of infusion should be the clinical impression of the labor and the progress made in cervical dilatation. It is to be emphasized, however, that the more misleading of the two is the clinical impression of the labor. Even though the contractions appear adequate, if there is no progression over a number of hours the rate should be slowly increased until clinical change begins to occur. We do not recommend a rate in excess of 30 drops per minute.

Each of our patients receiving a Pitocin infusion has a nurse in constant attendance. It is her duty to record at quarter-hour intervals the rate of infusion, the frequency, duration, and intensity of the contractions, the blood pressure, and the fetal heart rate. Any variations are immediately reported. Only the resident physician or attending physician is allowed to increase the rate of the infusion.

When the patient approaches second stage, especially the multipara, the infusion is frequently slowed down and even on occasion stopped entirely. This is done, particularly when the contractions are forceful, in an attempt to avoid a precipitate type of delivery. The infusion has been continued in some patients into the third stage after this temporary retardation.

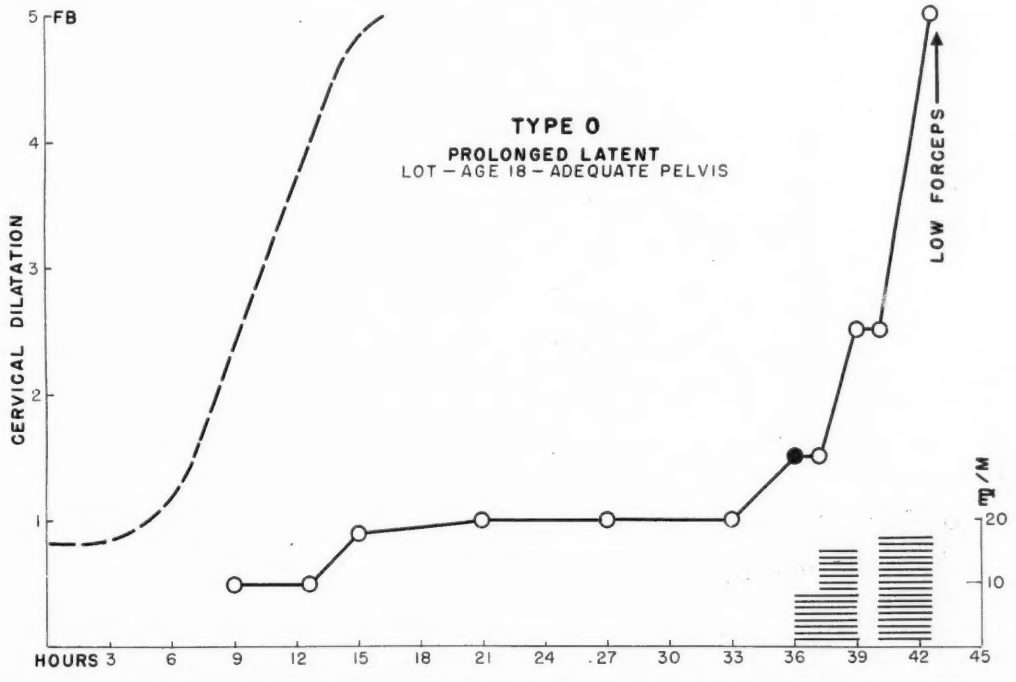


Fig. 3.—Type O. Prolonged latent period. Conversion: normal active labor. Relatively low dosage. A point of interest is that the infusion infiltrated and the Pitocin stimulation ceased for about an hour. During this time there was an arrest in cervical dilatation which was immediately corrected by the reinstitution of the infusion. Ordinate shows minims of Pitocin per minute and abscissa shows duration of infusion in hours.

Results

General.—

Of the 215 cases treated, 17 per cent were from the private service as compared with 38 per cent private patients in the entire obstetrical service. This may be related to a lower incidence of inertia among private patients or a greater reluctance to use the method in that group. The fact that no private patients were recorded as having Types 6, 7, and 8, in which atypical patterns

of labor follow prolonged latent periods, suggests also that the more serious forms of inertia on that service either did not occur or were treated by other means.

The primiparous patients, constituting 40.1 per cent of our service, accounted for 81 per cent of these cases. Of these, 31 per cent were over the age of 30 years. Since our over-all incidence of such elderly primiparas is 24 per cent, the prototype of the patients in this study is a primipara who tends to be older than the average and of the ward-service class. The patients were all at or near term except for 9 and in each instance these had premature rupture of the membranes. Patients who appeared with premature labor whose membranes were intact were treated conservatively with sedation.

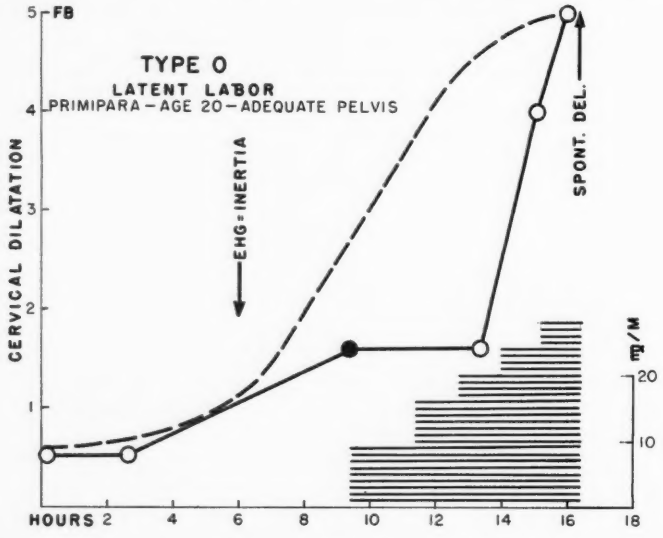


Fig. 4.—Labor was diagnosed as uterine inertia by the electrohysterograph before sufficient time had elapsed to make the diagnosis on clinical grounds. Note the amount of Pitocin needed to convert to a normal active type of labor. The last increment in the dosage rate was unnecessary. This error should be avoided.

The presentations in the patients treated included 11 breeches and 66 occipitoposteriors (30.77 per cent). The over-all incidence of the occipitoposterior position on our service during the period of study was 13 per cent. This indicates a greater tendency of the occipitoposterior to be associated with inertia than of the other vertex presentations.

TABLE II

TYPE OF LABOR	NO. OF PATIENTS
O*—PL	79
1—NL-NA	6
2—NL-NA-A	46
3—NL-PA	26
4—NL-PA-A	13
5—PL-NA	4
6—PL-NA-A	6
7—PL-PA	12
8—PL-PA-A	7
X*	16
	215

*Type O—Cases in which treatment was started in the latent phase before any pattern of labor was established.

Type X—Cases in which treatment was started in the second stage irrespective of the first stage pattern.

The distribution of cases according to various atypical patterns of labor is recorded in Table II. It will be noted that all types were represented including 6 of Type 1, which is an entirely normal pattern. Pituitrin might have been withheld from this small group had their labors been graphically analyzed.

An example of each type of labor with the conversion pattern brought about by intravenous Pituitrin is shown in Figs. 3-13. The significant clinical data relating to each are indicated in the legends.

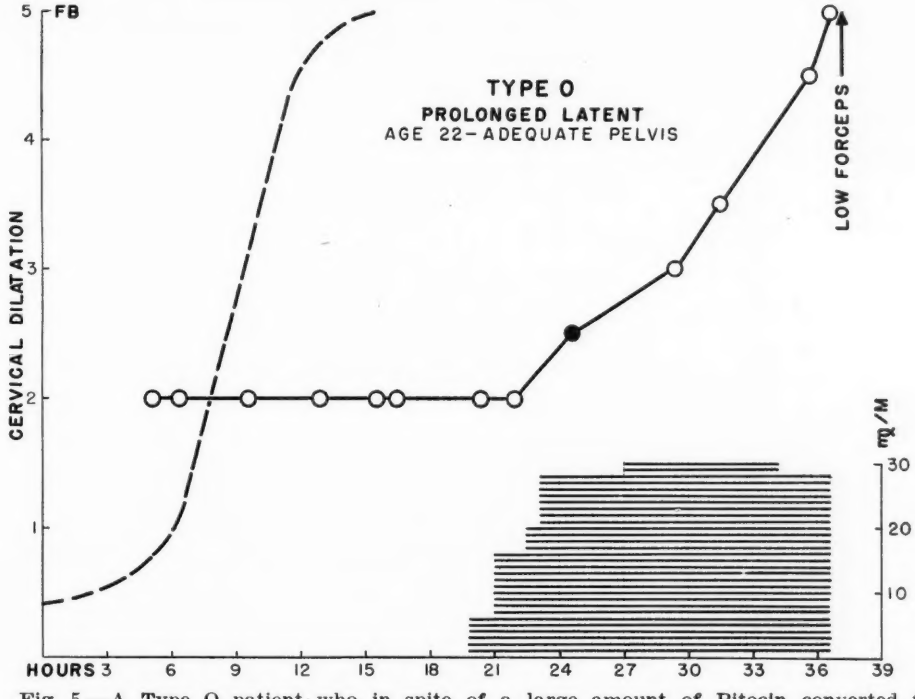


Fig. 5.—A Type O patient who in spite of a large amount of Pitocin converted to a prolonged-active rather than normal-active type of pattern. This type of conversion may still result in normal delivery.

Dosage.—

The effective infusion rate was 15 minims per minute or less in 57 per cent of the cases. We have been amazed at times at the small amount of Pitocin required to convert abnormal labor types into normal patterns. This is apparent in some of the graphs presented. On the other hand, failures invariably occurred when the infusion rate had to be raised to a point over 30 minims per minute.

A point of practical interest is that there is considerable individual variation in the response of the uterus to the drug. This requires a careful adjustment of the rate of infusion to meet the needs of each patient.

Effect on the Mother.—

The occurrence of tetanic contractions has been already mentioned as one of the complications of administering Pitocin during labor. This, in our experience, has occurred even with very low doses and is one of the reasons why these patients must be under constant observation. This complication was recorded in 4 cases. In one case the infusion was given after a seventeen-hour latent phase; tetanic contraction appeared at a dose of 8 drops per minute. The infusion was

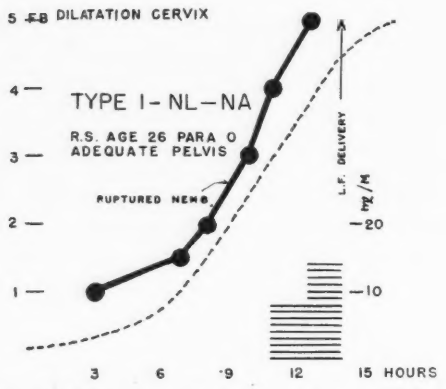


Fig. 6.—Type 1. Normal latent—normal active labor. While this patient's uterine contractions appeared weak and occurred infrequently, the pattern of labor was normal. There was no indication for the use of Pituitrin in this case.

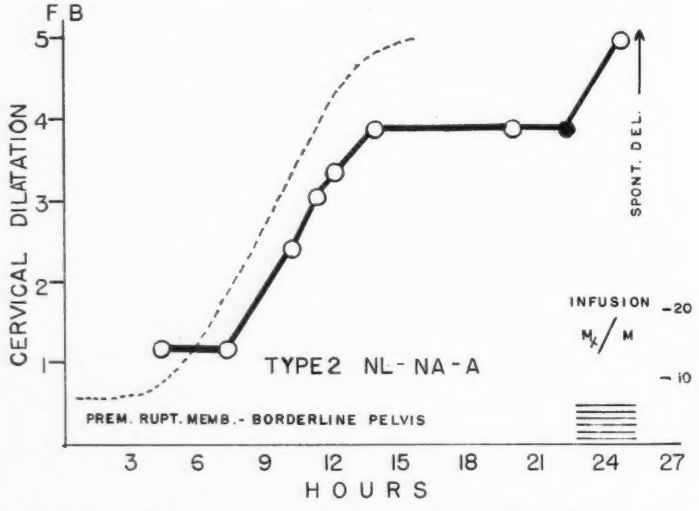


Fig. 7.—Type 2. Normal latent—normal active—arrested labor. Conversion pattern: normal active.

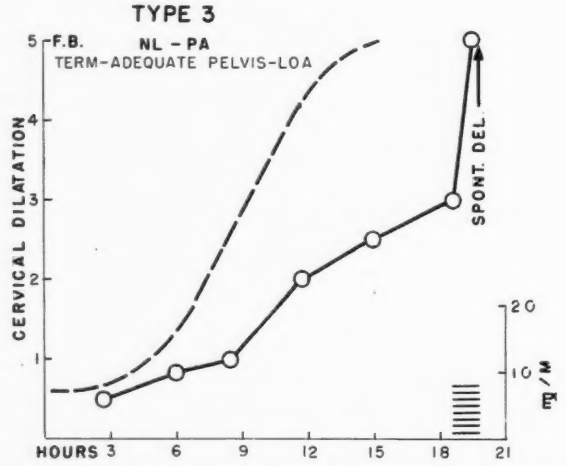


Fig. 8.—Type 3. Normal latent—prolonged active labor. Conversion: normal active labor.

discontinued and the patient proceeded into a normal active phase and delivered spontaneously. In 3 others the tetanic contractions appeared at rates between 5 and 9 drops per minute; in each instance the infusion was stopped, then restarted without further difficulty. In one of these the effective rate reached 35 drops per minute without causing further hypertonia. In one case a contraction ring developed after a nine-hour infusion which reached 28 minims per minute. This complication is reported by Labate and Barbaro[11] in 2 cases.

These same workers[11] reported 3 cases of edema of the cervix and suggested a possible relationship to a reversal effect. It is our belief that cervical edema, which we have also observed, is the mechanical result of a tight fit between the presenting part and the pelvic structures. It should be interpreted as a sign pointing to an abnormal cephalopelvic relationship rather than as the direct effect of Pituitrin.

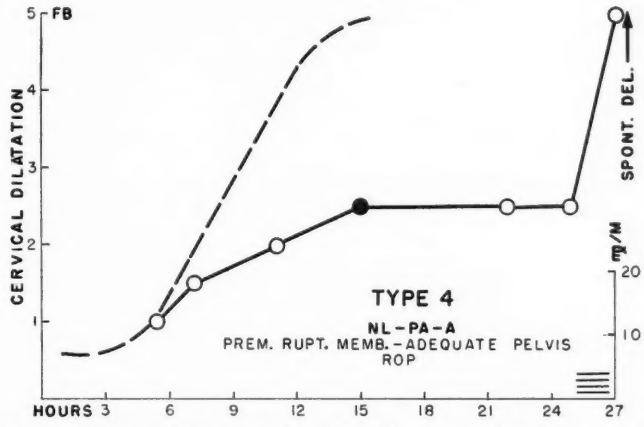


Fig. 9.—Type 4. Normal latent—prolonged active—arrested labor. Conversion: normal active labor. Note small amount of Pitocin required to convert arrested labor to normal pattern.

Postpartum hemorrhage of 250 to 500 c.c. occurred in 14.8 per cent and of 500 c.c. or over in 3.2 per cent of our cases. One of these patients developed a very atonic uterus that did not respond to any of the more conservative forms of treatment and required hysterectomy.

Our service incidence of postpartum hemorrhage of 250 to 500 c.c. is 12.0 per cent and of 500 c.c. or over is 1.3 per cent.

Comparison of postpartum hemorrhage on our obstetrical service and in the study group reflects the often-stated impression that there is slightly more postpartum blood loss in patients who receive stimulation of labor by intravenous Pitocin. While we are all anxious to accelerate these labors and accept this as desirable, we should recognize the fact that a rapid labor may be harmful in this respect. In addition, it should be pointed out that in the study group there was an increased incidence of operative deliveries with resultant cervical tears, deep episiotomies, and episiotomy extensions, which may have in themselves contributed to the increased blood loss.

There were 14 cervical tears. Three occurred spontaneously, the remainder were in association with instrumental deliveries.

Effect on Baby.—

The gross fetal mortality rate in this series was 3.25 per cent (7 deaths). This is corrected by eliminating 3 antepartum deaths; one hydrocephalic fetus; and one 800 gram previable premature fetus, leaving a corrected rate of 0.95 per cent. This appears unusually low considering the large number of patients with complicated labors.

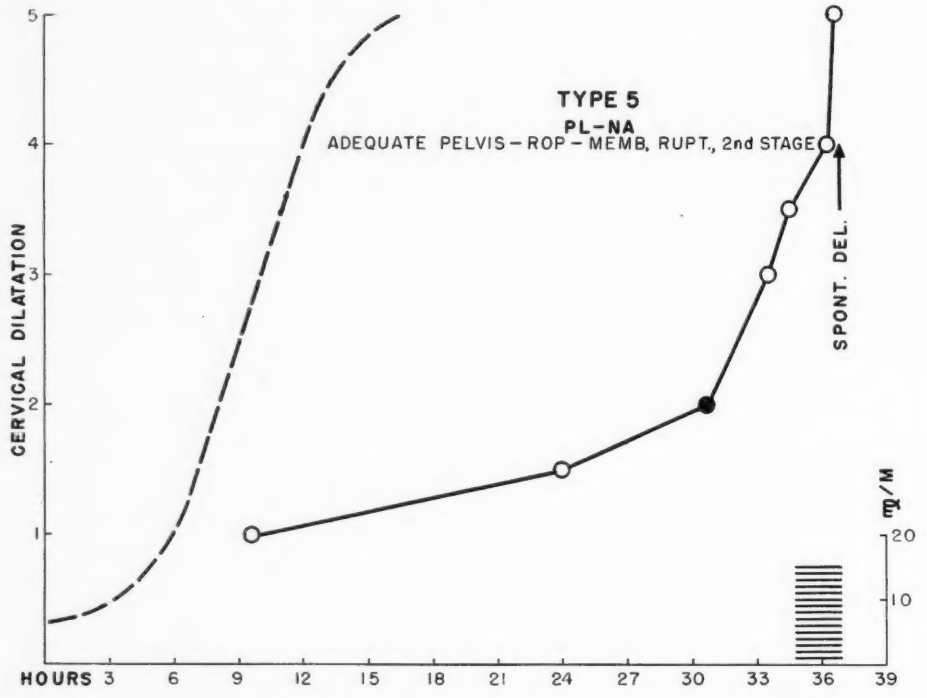


Fig. 10.—Type 5. Prolonged latent—normal active labor. Conversion of prolonged latent to normal active labor was not recognized, and Pituitrin was erroneously administered because of the long latent phase.

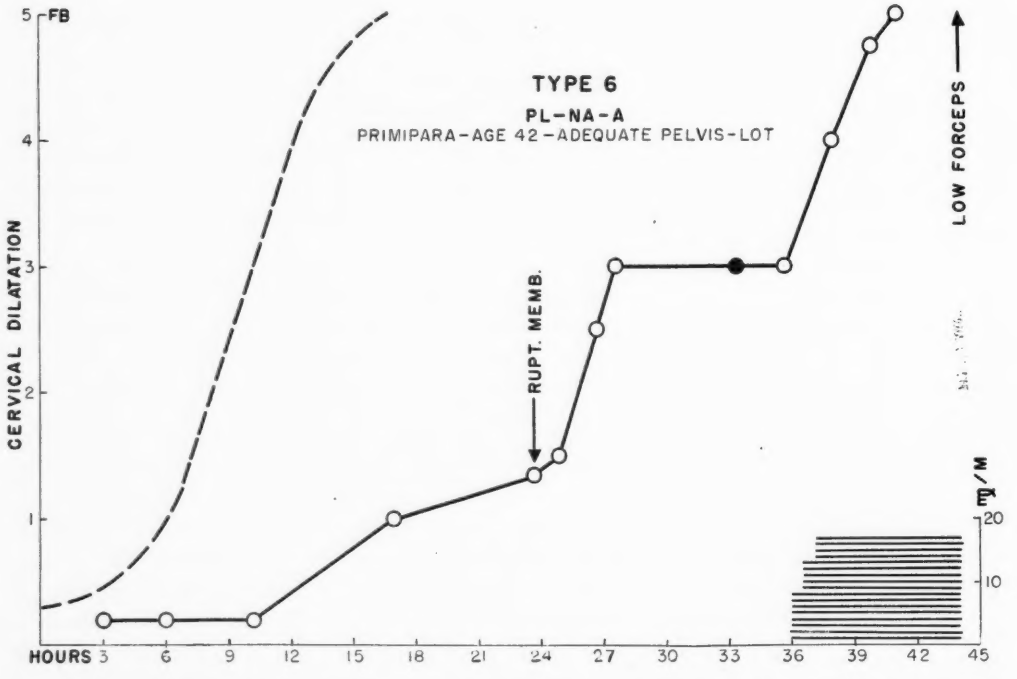


Fig. 11.—Type 6. Prolonged latent—Normal active—arrested labor. Conversion pattern: normal active labor. Note stimulating effect of rupture of membranes with subsequent arrest. Elderly primipara.

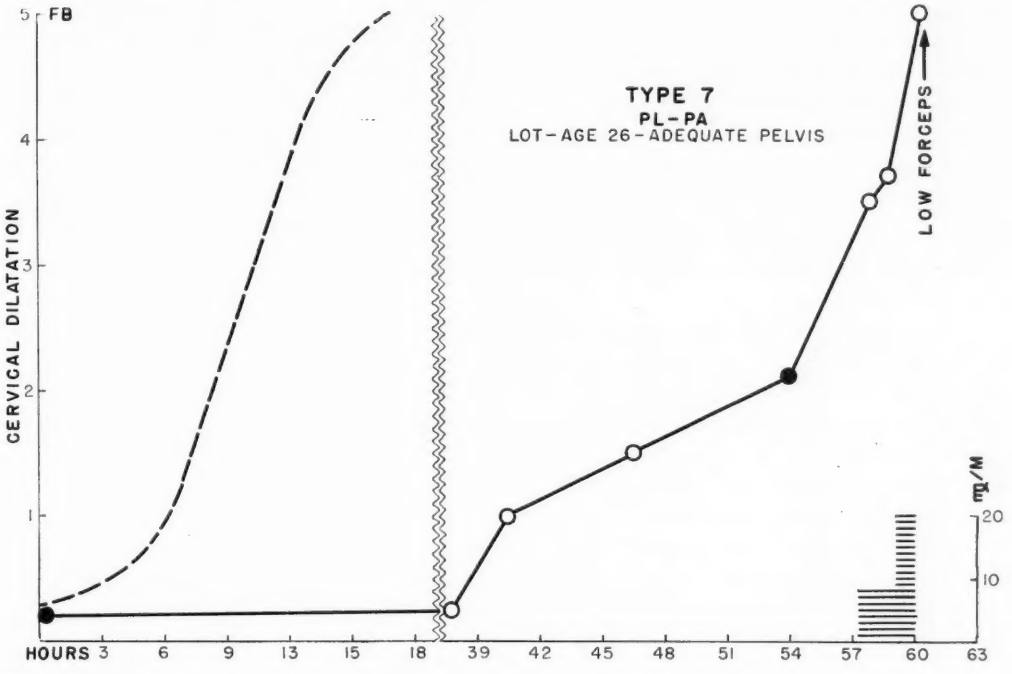


Fig. 12.—Type 7. Prolonged latent—prolonged active labor. Conversion: normal active labor.

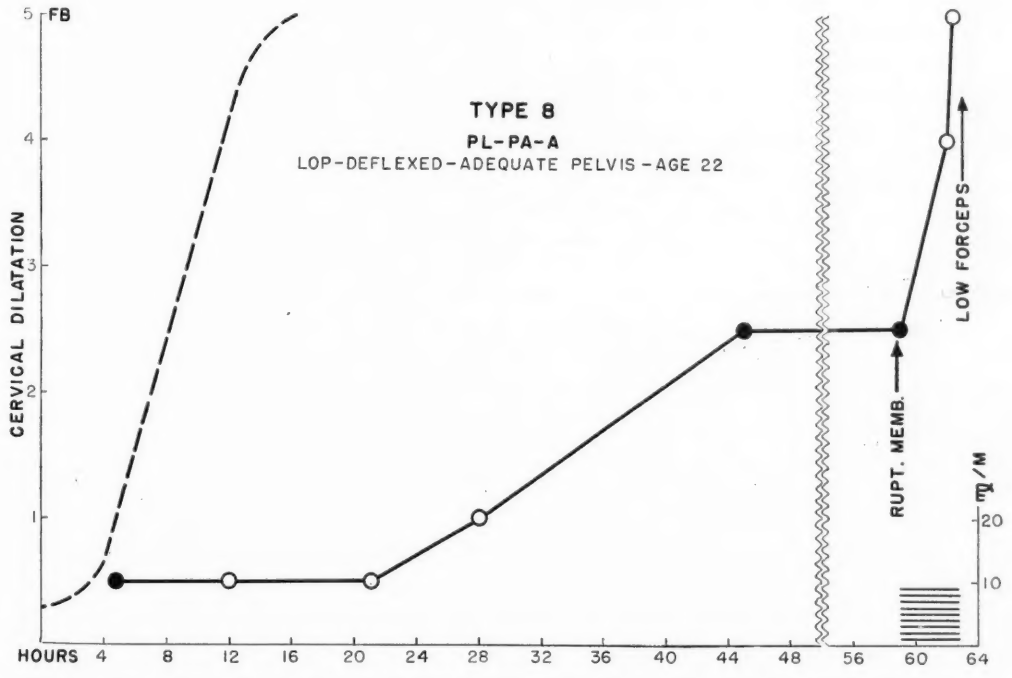


Fig. 13.—Type 8. Prolonged latent—prolonged active—arrested labor. Conversion: normal active labor. Note rupture of membranes at time the infusion began. It is difficult to determine whether rupture of the membranes or Pituitrin infusion is responsible for the stimulation of labor in these cases.

Fetal distress, apart from the 2 traumatic deaths, occurred in 3 cases. One of these was due to an occult prolapsed cord, while the other two were not explained. It is likely that transient fetal heart irregularities were not always recorded. Hellman[4] states that an irregular fetal heartbeat with slowing occurred in 10 per cent of his cases.

Resuscitation of the baby requiring more than purely routine measures was noted in 25 cases. This seems high, but since 20 per cent of these patients required some form of major operative intervention with the attendant prolongation of labor, analgesia, and anesthesia, this may not be far in excess of what might have occurred in a similar group of controls.

Failures.—

We calculated as our failures those cases in which delivery did not take place spontaneously or by low forceps. On this basis there were 43 (20 per cent). A more realistic failure rate is obtained by the elimination of 22 cases for the reason that the duration of administration or dosage or both was questionably adequate, or because obstetric interference was carried out for reasons other than the inertia when the latter had been overcome. The corrected failure rate was, therefore, 9.8 per cent.

A number of cases considered as failures by these criteria resulted in relatively simple midforceps delivery at a low station. These might well have been difficult deliveries had the patients not received Pituitrin, and in that sense could be considered successful cases. For the sake of uniformity, however, they have been included in the failure group.

Failures occurred in all the varieties of atypical labor. The only outstanding observation in this respect was the small number of failures in the patients who were treated for inertia occurring for the first time in the course of the second stage after a previously normal first stage.

We were unable to relate the success or failure of the method with either the duration of the total labor before treatment was instituted or the duration of the abnormal labor. We have calculated this on the basis both of all cases treated and of a more selected group in which Type O patients were excluded.

The relation of the intact or ruptured membranes to the success or failure of Pituitrin stimulation has been frequently raised. Gordon,[12] for example, stated that in primary inertia the rupturing of the membranes was a prerequisite for success. In our series the majority of the patients (167 cases) had ruptured membranes before the infusion was given and offer no basis for this part of the discussion. An analysis of the 48 (22 per cent) patients who had intact membranes when treatment was instituted shows that in 34 progress resulted from the infusion while subsequent rupture of the membranes produced no significant change; in 7, while some progress was evident from the infusion alone, a striking improvement in the labor pattern occurred following the rupture of the membranes. In an additional 7, no progress was evident until membranes ruptured or amniotomy was performed. We conclude from the data that the Pituitrin will initiate progress in the inert labor while the membranes are intact, but that amniotomy serves as a valuable adjunct to the success of the therapy.

There was no relation between the failure rate and the extent of dilatation of the cervix at the time therapy was initiated.

Conversion Patterns.—

The usual conversion pattern in 189 patients, who at the time of treatment were showing evidence of inertia and were in the first stage of labor, was the normal active type (80 per cent). In spite of this encouraging sign there was a

failure of 10.6 per cent in this group. This was due to the fact that, while full dilatation was obtained, arrest took place in the second stage, and delivery was accomplished by midforceps or cesarean section.

In the remaining 20 per cent the conversion pattern was abnormal (prolonged active, prolonged active arrested, normal active arrested, or continued arrest). Here the failure rate was 65.7 per cent. This striking figure indicates the serious implication of an abnormal conversion pattern. In particular, the arrested types of conversion in our cases were often associated with varying degrees of cephalopelvic disproportion.

Parenthetically it should be stated that an abnormal conversion pattern may be due to insufficient dosage rather than the complications before mentioned.

Borderline Pelves.—

An important aspect of this discussion is concerned with the patient who presents both uterine inertia and a borderline degree of pelvic contraction. That the Pituitrin infusion is of value in the management of these cases has been attested by Cosgrove,[13] Stone and Tanz,[14] and Lubin and his co-workers.[15]

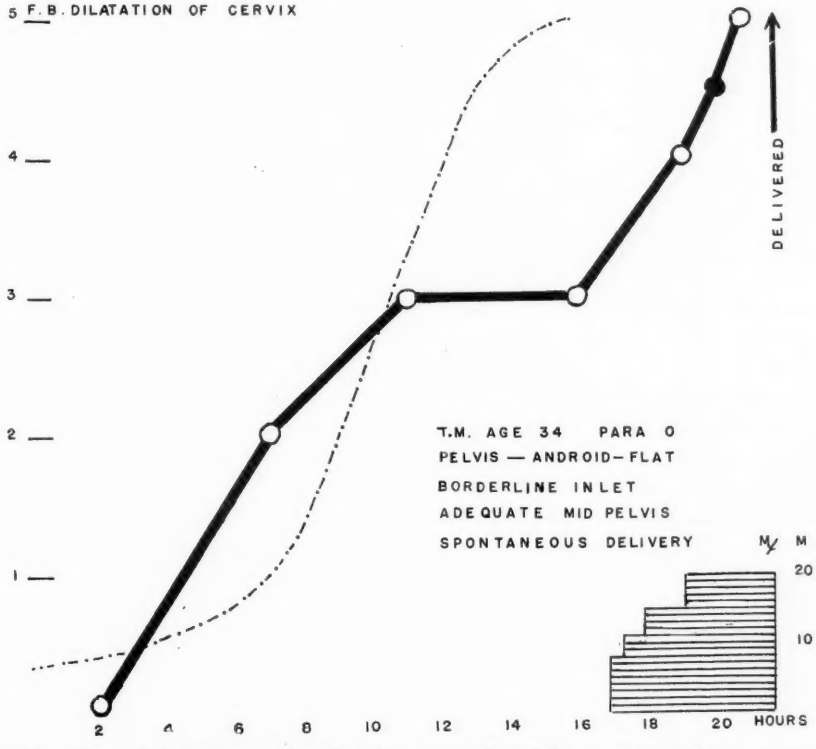


Fig. 14.—Normal latent—prolonged active—arrested labor. Conversion: normal active labor. Pelvic contraction was at inlet. The ideal case of relative cephalopelvic disproportion for a trial with Pituitrin infusion.

Labate and Barbaro,[11] although reporting 12 midforceps deliveries and one cesarean section in a total of 36 cases of inertia, stated that they excluded the borderline pelvis from their treated cases. What appears to be an apparent inconsistency in their statement is mentioned here simply to point out the fact that there may be considerable difference of opinion as to what constitutes a borderline cephalopelvic relationship.

In this series 38 patients were classified as having borderline pelves on the basis of both clinical and x-ray examination. These were essentially cases in which a trial of labor was advised.

An analysis of our material leads us to take the position of both advocating and discouraging its use in such cases, the decision being related in the main to the specific areas of pelvic contraction, as we will show.

TABLE III

BORDERLINE DISPROPORTION	TOTAL	SPONTANEOUS OR LOW FORCEPS	MIDFORCEPS UNCOMPLICATED	MIDFORCEPS DIFFICULT	CESAREAN SECTION	VERSION	BREECH DELIVERY
At inlet only	13	8	2	0	2	1	0
At midpelvis only	18	4	8	2	3	0	1
Inlet and midpelvis	7	0	2	2	3	0	0
Total	38	12	12	4	8	1	1

It will be noted from Table III that of the 13 cases in which the disproportion occurred at the inlet only, eight were delivered spontaneously or by low forceps. Two others were delivered by easy midforceps. There were no difficult midforceps. The 2 cesarean sections were done for a contraction ring in one case and in the other for failure to advance in an elderly primipara after a half-hearted attempt to correct the inertia. One version was done resulting in a stillbirth after an unfortunate prolapse of the cord which occurred in the course of a midforceps delivery. This group, with inlet contraction alone, proved to be our most favorable for treatment. Of interest is the fact that the dosage required was often minimal. The classical type here is the patient with a flattened inlet and the head at a relatively high station that requires extra drive to advance it beyond the inlet to the adequate lower pelvis (Fig. 14). While this was the characteristic mechanism in the rachitic pelvis of a generation ago, it has its counterpart in such purely morphologic variants as the platypelloid pelvis and the gynecoid-flat pelvis with adequate lower pelvic capacity.

In contrast to this type were the 25 patients with either midpelvic contraction alone or midpelvic contraction associated with inlet contraction (Figs. 15 and 16). Only 4 of these were delivered spontaneously or with low forceps, the remainder requiring midforceps or cesarean section. Four of the midforceps deliveries in this group were difficult. It is likely that had these patients not received Pituitrin they would have been delivered by cesarean section, in which case one baby would have been spared and all the mothers saved from considerable trauma. It is a tribute to the good judgment of the staff that in 7 of the 8 cesarean sections done in this group they had the courage to admit failure and resort to a cesarean section, even after a long labor with arrest. The safety of the cesarean section when all the available supportive and infection-preventing measures are added to it often makes such a final choice of management a wise one. Since 10 of the 25 patients were delivered by uncomplicated midforceps operations, however, it is apparent that the contracted midpelvis is a matter of degree which is not always ascertainable.

We conclude by urging the use of Pituitrin infusions in all cases of inertia requiring a test of labor if the borderline contraction is at the inlet only, but great selectivity about cases of midpelvic contraction, reserving Pituitrin only for those with lesser degrees of such contraction. There is safety in treating the patient with inlet contraction, for the ultimate delivery terminates either easily from below or by cesarean section. The patient with the contracted midpelvis, on the other hand, presents a trap literally and figuratively for both the baby and the obstetrician.

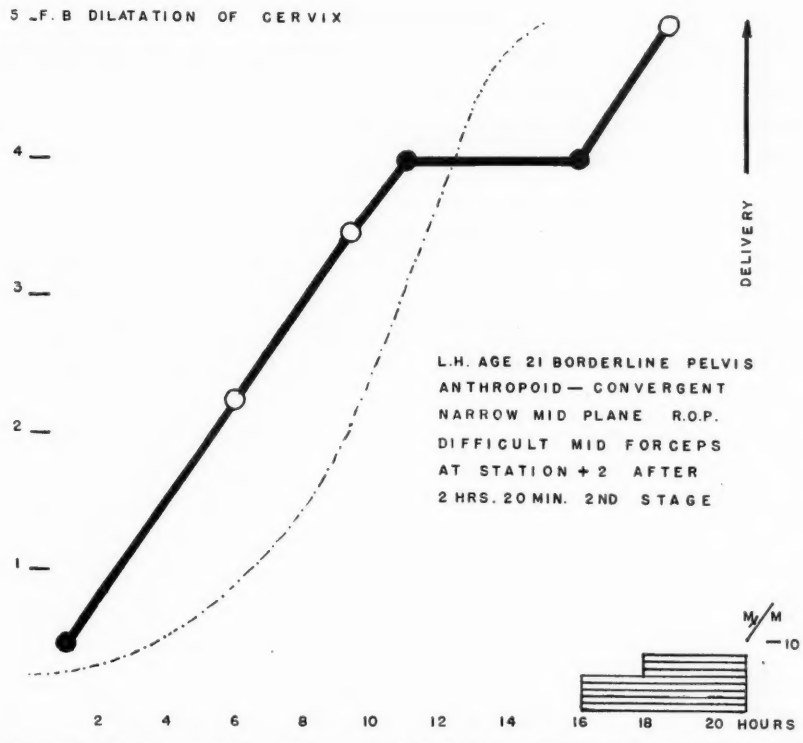


Fig. 15.—Normal latent—normal active—arrested labor. Conversion: normal active labor. Mid-pelvic contraction. Unfavorable candidate for Pituitrin infusion.

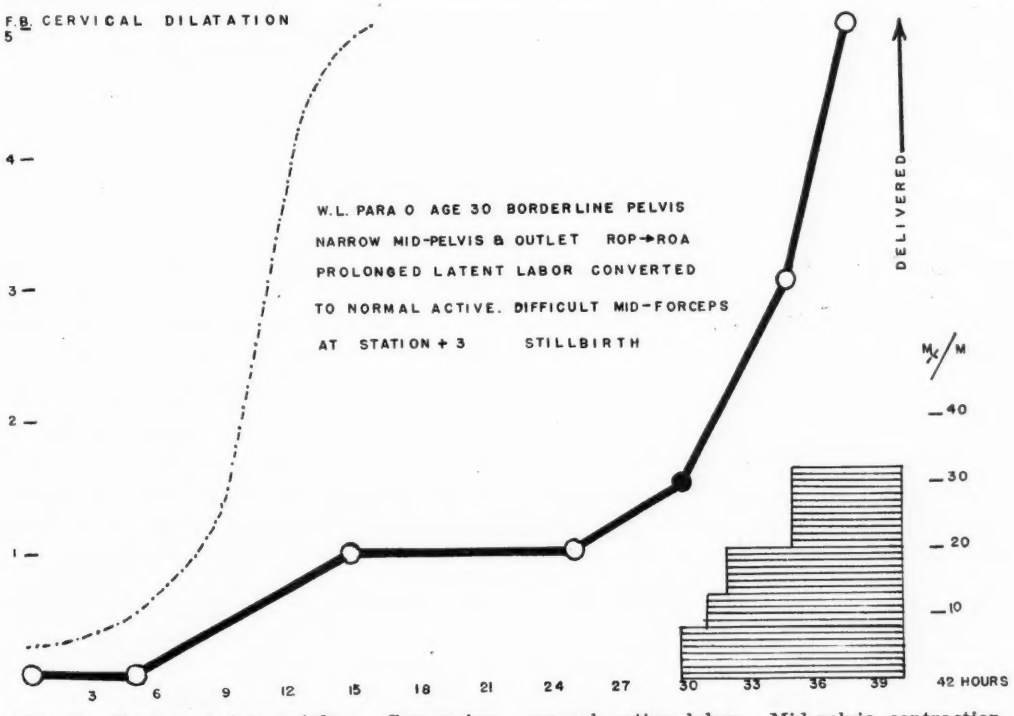


Fig. 16.—Prolonged latent labor. Conversion: normal active labor. Mid-pelvic contraction. Unfavorable candidate for Pituitrin infusion.

Summary

1. Two hundred and fifteen cases of uterine inertia treated intravenously with dilute posterior pituitary extract at the Sloane Hospital from May, 1948, to September, 1953, have been reviewed.

2. Patients were found to be predominately from the ward service with only 17 per cent from the private service, as compared with 38 per cent private patients in the entire obstetrical service.

3. Eighty-one per cent of patients were primiparas, compared with a service incidence of 41 per cent. Of these, 31 per cent were over the age of 30, our over-all incidence of such elderly primiparas being 15.24 per cent.

4. There were only 9 premature labors in the group, all with ruptured membranes.

5. The presentations included 138 occipitoanterior or occipitotransverse, 66 occipitoposterior (30.77 per cent), and 11 breech. The over-all incidence of the occipitoposterior on our service is 13 per cent. There were 3 sets of twins.

6. The effective infusion rate was 15 drops per minute or less in 57 per cent of the patients.

7. Tetanic contraction was recorded in 4 cases, in 3 of which the infusion was temporarily discontinued, then restarted without further complications.

8. One patient developed a contraction ring.

9. Postpartum hemorrhage of over 500 c.c. occurred in 3.2 per cent, as compared to our service incidence of 1.3 per cent.

10. There were 14 cervical tears; 3 were in spontaneous deliveries.

11. The gross fetal mortality rate was 3.25 per cent, with a corrected rate of 0.95 per cent.

12. Fetal distress, apart from the 2 deaths from trauma, occurred in 3 cases—one from an occult prolapsed cord, and 2 unexplained.

13. Resuscitation of the baby requiring more than purely routine measures was necessary in 25 cases.

14. The gross failure rate was 20 per cent with a corrected failure rate of 9.8 per cent.

15. There was no evident relationship between the success of the infusion and the duration of total labor or abnormal labor before treatment was started.

16. In 77.6 per cent of cases the treatment was started after the membranes had ruptured. Of the remaining 48 patients, there was no progress in 7 until the membranes ruptured and 7 showed striking improvement of a slow progressive pattern following rupture; in the remainder, rupture of the membranes had little effect on the pattern of labor already established by the Pitocin.

17. No relation was noted between the failure rate and dilatation of the cervix at the time of therapy.

18. The usual conversion pattern (80 per cent) in 189 cases was normal active with a failure rate of 10.6 per cent. The conversion pattern in 20 per cent was abnormal with a failure rate of 65.7 per cent.

19. Borderline pelves are no contraindication to the use of the Pituitrin infusion but pelves with midpelvic or midpelvic and inlet contraction, with a failure rate of 84 per cent, should be carefully selected.

We gratefully acknowledge the technical assistance of Belle Rojowski, R.N., Rita Ruane, R.N., and Mary Souter, R.N.

References

1. Page, E. W.: Proc. Soc. Exper. Biol. & Med. **52**: 195, 1943.
2. Theobald, G. W., Graham, A., Campbell, J., Gange, P. D., and Driscoll, W. J.: Brit. M. J. **2**: 123, 1948.
3. Hellman, L.: Am. J. Obst. & Gynec. **57**: 364, 1949.
4. Hellman, L., Harris, J. S., and Reynolds, S. R. M.: Am. J. Obst. & Gynec. **59**: 41, 1950.
5. Stone, M. L.: Am. J. Obst. & Gynec. **59**: 49, 1950.
6. Reynolds, S. R. M., Heard, O. O., Bruns, P., and Hellman, L. M.: Bull. Johns Hopkins Hosp. **82**: 446, 1948.
7. Steer, C. M., and Hertsch, G. J.: Am. J. Obst. & Gynec. **59**: 25, 1950.
8. Friedman, E. A.: Am. J. Obst. & Gynec. **68**: 1568, 1954.
9. Schmitz, H. E., Bremner, J. X., Towne, J. E., and Baba, G. R.: Am. J. Obst. & Gynec. **54**: 643, 1947.
10. Hallet, R., and Burgess, S.: Personal communication.
11. Labate, J. S., and Barbaro, A. J.: Am. J. Obst. & Gynec. **62**: 1292, 1951.
12. Gordon, C. A.: Am. J. Surg. **82**: 76, 1951.
13. Cosgrove, S. A., and Burnett, L. F.: J. Michigan M. Soc. **50**: 33, 1951.
14. Stone, Martin C., and Tanz, Alfred: Obst. & Gynec. **1**: 346, 1953.
15. Lubin, S.: Am. J. Surg. **81**: 509, 1951.

Discussion

DR. LOUIS M. HELLMAN (as read by DR. J. EDWARD HALL).—It has become increasingly clear that, while complicated machines can delineate varying types of uterine malfunction, these are not of great help to the physician observing the actual process of parturition. The designations of primary and secondary uterine inertia are likewise unclear. In looking back over what has been written during the past six or seven years, it becomes obvious that all of us who deal with this subject are beginning to think of uterine dysfunction in terms of cervical dilatation as a function of elapsed time. I wish that I had been astute enough to draw the curves as Friedman did or to delineate from them the types of abnormality as clearly as the present authors. I agree with Dr. Moore's definition of false labor. While this diagnosis must be made after the fact, it nevertheless is clear-cut. The misleading term "prodromal labor" disappears in Dr. Moore's latent period. Uterine dysfunction now becomes clearly and understandably divided into three categories. The treatment of abnormalities in the latter two phases, namely, prolongation of the acceleration and deceleration phases, is in general well accomplished with Pitocin. Not so, however, abnormalities in the latent phase. I cannot tell from the authors' statement whether they have actually had bad results in treating this entity with pituitary extract or whether they think they might have. This is the old and admittedly poorly defined entity of primary inertia.

In the last 6,100 deliveries in our clinic we have seen 59 instances of this undesirable phenomenon. In 9 cases Pitocin was given, with a fetal loss rate of 11 per cent and a cesarean section rate of 22 per cent. In 50 cases we gave no Pitocin, losing 6 per cent of the babies and sectioning 28 per cent of the mothers. Other than the fact that such uterine dysfunction is frequently associated with borderline pelves, we know little of either the cause or the results. I suspect, as do the authors, that prolongation of the latent phase is of serious import, whether it be treated with oxytocin or not.

In talking about our fetal deaths we should deal with the uncorrected figure. Any obstetrician worthy of his salt can correct his mortality figures to the disappearance point. Dr. Moore's gross mortality figure of 3.25 per cent is extraordinarily low considering the

serious nature of the complications with which he is dealing. Ours, in the last 101 cases of secondary uterine inertia, is 7.9 per cent, a figure which, while not statistically greater because of the small number of cases, does in actuality appear to be somewhat larger.

I find myself in only one point of major disagreement with the authors. That concerns the employment of Pitocin stimulation in the face of borderline pelvic contractions. Even with the best facilities and great knowledge concerning the pelvis, such as is available to Dr. D'Esopo, we can define accurately only the morphology of the pelvis and its crucial diameters. Accurate or reasonably accurate knowledge of fetal head size so far has eluded us. How far we can be wrong is illustrated in the case of a young primigravida whose pelvic inlet measured 9 cm. in the anteroposterior diameter by 11.2 cm. in the transverse. When the obstetrician was faced with uterine inertia with an estimated 2,800 gram fetus he elected to stimulate labor with Pitocin, feeling quite naturally that with good pains this small infant should pass the borderline inlet easily. Delivery was accomplished by cesarean section. Although the infant weighed only 2,880 grams the biparietal measurement of the head was 10.2 cm., a fact missed by both clinician and x-ray alike. Perhaps no harm was done here but what of a slightly smaller head, forced successfully through a tight fit? The bad results may not show in the infant mortality results as they fail to show in Dr. Moore's figures. The long-term results may be of serious import nor can one quite ignore the possibility of rupture of the uterus, which not only can but does occur. At the risk of being considered quite unprogressive, I would like to state that in my opinion the treatment of uterine inertia in the face of contracted pelvis, be it borderline or absolute, is still cesarean section.

DR. CHARLES STEER.—I have been able to study 556 cases of labor of various sorts with the Electrohysterograph, of which 51 cases were diagnosed clinically as uterine inertia. Among these 51 cases, there were 5 patients who had no electrical activity. Two of these had in addition a considerable element of cephalopelvic disproportion. All of these 5 required cesarean section. Three of these had Pitocin infusions for varying periods of time but in all 3 it was felt by the observer that an adequate trial had been given to the Pitocin infusion. On the other hand, 46 of these patients (of whom 39 had been on Pitocin infusion) were delivered safely from below, and all of these 46 had electrical activity of one sort or another.

It is my feeling from studying these cases with the Electrohysterograph that the cases of true primary uterine inertia represent a basic abnormality of uterine muscle-fiber function. These cases can be differentiated by electrical means, but they are also the ones that differentiate themselves with the Pitocin infusion—where no cephalopelvic disproportion exists, and where the Pitocin infusion does not give cervical dilatation in spite of active uterine contraction. This type of thing exists and failure must be confessed.

DR. D'ESOPO (Closing).—In reference to the results obtained in those cases that were treated during the latent phase, our failures amounted to about 14 per cent; the results were generally good. Paradoxically, the later these patients are treated, the higher the incidence of success, for the reason that when you treat them early you may be dealing with patients in false labor rather than latent labor and these are often unsuccessful.

When these data were reviewed, it was difficult for me to believe that in a group of 215 cases of this type we could achieve such a good record, especially with respect to the fetal deaths. It was difficult because in my own mind I kept constantly thinking of some of our old experience with intramuscular Pituitrin, or when we did not use any Pituitrin at all; it seemed hardly possible that we could now have such a difference in end results. In particular I had in mind some of the cases with fetal death that Dr. Marchetti and I reported from the Cornell Service, and our own service beween 1935 and 1940. One of the conclusions we reached at that time was that Pituitrin in labor should be used very sparingly, if at all.

While I am sure that the good end results reported here were due in part to a freer use of abdominal section and a diminished incidence of traumatic vaginal interference in the cases that we have listed here as failures, a great deal of credit must go to the therapy

itself. Often it had the effect of converting a difficult labor into one that terminated rather easily by natural delivery. This is a real tribute to those who were instrumental in proposing this method, and it has taken Pituitrin in labor out of the class of dangerous drugs and put it into the useful and desirable class.

There are two errors that I think can be made with Pituitrin when given in this way. First, we must be sure that we are not changing the inert labor to an overactive one—a labor with explosive activity, with its resulting trauma and hemorrhage. This may result even with infinitesimal amounts of Pituitrin. We are so enthusiastic about the change of an inert labor into an active one that we hesitate to put on the brakes. The other error has to do with the borderline contracted pelvis. Dr. Hellman mentioned in his discussion that this is a contraindication. We, on the other hand, used Pituitrin in these cases where a trial of labor was indicated. A borderline pelvis is not easily defined. The difference between Dr. Hellman's point of view and ours is probably more a matter of terminology than of principle. Frequently a patient with borderline contraction is better off if she has inertia; it would almost appear to be a protective mechanism. We certainly must avoid in particular the patient with the midpelvic contraction, for here we may get into a situation from which it is difficult to retreat back to safe ground.

ADEQUATE DOSAGE OF DILUTE INTRAVENOUS PITOCIN IN THE TREATMENT OF POSTPARTUM UTERINE ATONY*

AUGUST F. DARO, M.D., HARVEY A. GOLLIN, M.D., ERNEST G. NORA, JR., M.D.,**
CHICAGO, ILL., AND LEOPOLDO FREZZINI, M.D., MILAN, ITALY

(From the Department of Obstetrics and Gynecology, Cook County Hospital and Columbus Hospital, Chicago, and the University of Illinois College of Medicine, Department of Obstetrics and Gynecology)

THE use of dilute intravenous posterior pituitary extract (Pitocin) for the control of postpartum bleeding due to uterine atony has been found to be very effective in preventing excessive blood loss.[1] In certain instances it has precluded the use of heroic measures (hysterectomy, ligation of the uterine arteries, etc.) for the prevention of maternal death. Frequently the dose of the drug has been inadequate to gain the maximum benefit.

To review briefly the anatomy and physiology involved in this condition: The wall of the uterus is composed of three layers of tightly interwoven muscle fibers. The outer and inner layers are relatively thin, composed of fibers which run longitudinally through the wall. The median layer is much thicker, being made up of circular fibers which run in a more or less oblique course, and is very vascular. The three layers of muscular tissue are laced together by many intervening muscle strands and as a result of the crossing and recrossing of these fibers and muscle bundles a complex network is formed, enmeshed within which the many blood vessels course.

The normal mechanism which controls uterine bleeding is the contraction and retraction of these many interlacing muscle bundles and fibers. Contraction of this complex network constricts the blood vessels and uterine sinuses almost as if they had been ligated.[2] Normally this will completely inhibit any bleeding following the delivery of the placenta but it will not permanently stop the bleeding, because no muscle can remain constantly in a state of contraction. It is the ability of the uterine muscle to retract and thus permanently shorten itself which normally keeps the uterus firm and the blood vessels hemostatic. If the uterine musculature is atonic and uterine retraction slow, hemorrhage will ensue as soon as the uterus relaxes.

When postpartum bleeding occurs, the first procedure is to determine the cause, while the patient is being prepared for transfusion. Lacerations of the genital tract and the presence of retained placental tissue having been ruled out, oxytocics should be administered. As has been noted with the use of posterior pituitary extract for the induction of labor, or in the management of prolonged labor on the basis of uterine atony, varying doses of the drug are required for the desired effect.[3] This same variation exists in the use of the drug for the treatment of postpartum uterine relaxation.

*This investigation was supported by a research grant from the Dr. Jerome D. Solomon Research Foundation, Hektoen Institute for Medical Research.

**Stritch School of Medicine, Loyola University.

Ten minims of posterior pituitary extract in 1,000 c.c. of fluid, at a varying rate of drip, is the usual dilution used for induction of labor and treatment of inadequate contractions during labor. This dilution has been found, in many instances, to be inadequate for sufficient stimulation of the uterus to control postpartum hemorrhage and the dilution was varied to meet the needs of the individual case. The preparation found to be adequate in most instances is 2 c.c. (20 units) of posterior pituitary extract to 1,000 c.c. of 5 per cent glucose in water, the rate of drip being varied from 20 to 60 drops per minute. Even this solution has not been completely effective in certain cases, particularly following severe abruptio placentae or other instances of severe atony, and in these instances the amount has been increased to as much as 4 c.c. of Pitocin to 1,000 c.c. of fluid.

The increased amount of posterior pituitary extract is found to be preferable also in instances where prolonged administration of oxytocics is desirable in order to control the amount of fluids being administered to prevent overloading of the vascular system. The higher concentration is administered at a rate of drip sufficient to supply adequate stimulation of the uterus.

In cases where blood was being administered for excessive hemorrhage, posterior pituitary extract was added (1 or 2 c.c. to 500 c.c. of whole blood) with excellent effect in most instances.

Summary of Case Reports

CASE 1.—L. B., a 16-year-old gravida i, para 0, at term, was admitted with moderate vaginal bleeding. She appeared very pale, with a blood pressure of 110/70, and pulse 90 per minute. The fetal heart tones were not audible. The uterus remained contracted. There was 4 plus albuminuria. The patient was seen in consultation and a diagnosis of abruptio placentae was made. A sterile vaginal examination showed the cervix to be 2 cm. dilated, partially effaced, and the station of the head to be minus 2. The membranes were artificially ruptured. A transfusion of 1,000 c.c. of blood was given and the blood pressure was noted to be 160/110. The patient progressed in labor and after 6 hours delivered a stillborn infant. The placenta was expelled immediately, followed by many old blood clots and fresh bright red blood. Whole blood with 2 c.c. Pitocin to 500 c.c. was given and the bleeding was controlled. The following fluids were given intravenously over a period of twenty-four hours post partum:

1,000 c.c. 5 per cent glucose in water plus 3 c.c. Pitocin.
1,000 c.c. of whole blood plus 4 c.c. Pitocin.
1,000 c.c. 5 per cent glucose in water plus 3 c.c. Pitocin.

The uterus remained contracted and the bleeding was completely controlled. The patient had a good postpartum course, except for an elevated temperature for four days.

CASE 2.—L. P., a 35-year-old woman, gravida iii, para ii, at term, was admitted in good general condition with a normal temperature, blood pressure 120/80, and fetal heartbeat 136. She was in labor four hours during which time there was a great deal of bright red bleeding. She had a normal, spontaneous delivery. The placenta was expelled immediately, followed by fresh red blood and some old clots. Five hours later, the patient was in poor general condition (blood pressure 68/40, pulse 120, very weak). A transfusion of 1,000 c.c. of blood was given. The bleeding persisted in spite of repeated doses of Ergotrate intravenously and intramuscularly. The patient was seen in consultation eight hours after the delivery and a sterile vaginal examination showed the cervix to be intact, a superficial vaginal laceration which did not bleed, and the uterus intact and soft. The urine examination

showed 4 plus albumin. One thousand cubic centimeters of 5 per cent glucose in water plus 3 c.c. of posterior pituitary extract (Pitocin) was administered intravenously, followed by 1,000 c.c. of whole blood plus 4 c.c. Pitocin. Fourteen hours later the general condition was much improved, the blood pressure was 110/80, and the hemorrhage completely controlled. The Pitocin solution was continued constantly for forty-eight hours post partum. The patient had another 1,000 c.c. of blood and she left the hospital seven days later after a good postpartum course. This probably was another instance of premature separation of the placenta.

CASE 3.—R. G., a 26-year-old woman, gravida ii, para i, was admitted at term. A rectal examination showed station 0, dilatation 3 cm. She had irregular and weak contractions. Ten minims Pitocin to 1,000 c.c. 5 per cent glucose in water was given; the patient progressed in labor and had a normal spontaneous delivery. The placenta was expelled intact. Three hours later she had a profuse vaginal hemorrhage (the blood pressure was 80/50, pulse 120, and she was in poor general condition). The uterus was palpably atonic. She was given 1,000 c.c. of 5 per cent glucose in water plus 2 c.c. Pitocin intravenously, followed by 500 c.c. of whole blood plus 1 c.c. Pitocin and 1,000 c.c. of 5 per cent glucose in water plus 2 c.c. Pitocin. The hemorrhage was controlled and the patient left the hospital after five days in good general condition.

CASE 4.—C. M., was an 18-year-old woman, gravida i, para 0, at term. She was in labor fourteen hours and was delivered with low forceps. Fifteen minutes later, before the placenta was expelled, a profuse hemorrhage started and her blood pressure went down to 70/30. Pitocin, 2 c.c. in 1,000 c.c. 5 per cent glucose in water was immediately started intravenously, while the placenta was manually extracted. With the addition of 500 c.c. of whole blood plus 2 c.c. Pitocin the hemorrhage was controlled. Two hours later her blood pressure was 110/60 and the general condition satisfactory. The patient was discharged six days later after a good postpartum course.

Conclusions

1. The dose of posterior pituitary extract for control of postpartum hemorrhage on the basis of uterine atony must be varied to meet the needs in the individual case.

2. Concentration of posterior pituitary extract (4 c.c. to 1,000 c.c. of fluid) may be used at a slower drip (depending on individual requirement) for prolonged stimulation, where excessive administration of fluid is feared.

3. Posterior pituitary extract may be diluted in whole blood when the simultaneous effect of both is desired.

References

1. Daro, A. F., Gollin, H. A., and Lavieri, V.: AM. J. OBST. & GYNEC. **64**: 1163, 1952.
2. Greenhill, J. P.: The Principles and Practice of Obstetrics, originally by Joseph B. DeLee, ed. 10, Philadelphia, 1951, W. B. Saunders Company.
3. Daro, A. F., and Gollin, H. A.: AM. J. OBST. & GYNEC. **62**: 516, 1951.

Department of Case Reports
New Instruments, Etc.

OCCULT RUPTURE OF UTERUS FOLLOWING RUPTURED INTERSTITIAL PREGNANCY

JOHN H. MALFETANO, CAPTAIN, USAF (MC), GREAT FALLS AIR FORCE BASE, MONTANA

INTERSTITIAL pregnancy is a relatively rare entity. Wynne[2] reviewed the data on 2,405 ectopic pregnancies and found only 40, or 1.66 per cent, of the interstitial type. Most writers state that 0.5 to 1.3 per cent of pregnancies are extrauterine. Of this group, 0.65 to 2 per cent are of the interstitial variety.

The rupture in true interstitial pregnancy involves neither the oviduct or its insertion. Usually the laceration is below and slightly off the lateral uterine wall. Because of the arterial bleeding, immediate surgery is required. Most gynecologists perform hysterectomies for this condition; there has been little opportunity, therefore, to study succeeding pregnancies following repair of the laceration. Rupture during labor might be the only evidence of a defect in uterine healing. Such a case with its final outcome is reported here.

On March 14, 1953, a 30-year-old white woman, the mother of three children, was first admitted to a hospital in the Philippine Islands in profound shock. The last menstrual period had occurred on Oct. 24, 1952. The patient had complained of lower abdominal crampy pain on numerous prenatal visits, but now experienced sudden severe lower abdominal pain and syncope. Physical examination showed an unobtainable blood pressure, pulse 140, and a barely responsive patient. The abdomen was moderately distended, and a fluid wave was present. The uterus was palpable two fingerbreadths below the umbilicus. Bowel sounds were absent, as was the fetal heart beat.

An immediate operation disclosed the peritoneal cavity to be filled with fresh and old blood estimated at 3,000 c.c. The uterus, which was the size of a five months' normal pregnancy, seemed markedly softened and friable with fetal parts protruding from the right posterolateral wall. The dead fetus, the size of a twenty weeks' gestation, was delivered and the placenta easily detached. The right oviduct seemed to be intact.

In resection of the large laceration, the right oviduct and adjacent cornual region were removed and repaired with interrupted mattress sutures. After a rapid closure of the abdomen, the blood pressure rose to 60/40 and the pulse rate dropped to 100. A total of 10 units of blood was administered during the operative procedure and ensuing period. The postoperative course was stormy, with fever, râles in both lung fields, and bloody sputum. The patient was treated with large doses of antibiotics and careful control of the fluid balance. She was discharged in good condition on the eighteenth postoperative day. Future childbearing was discussed but not advised.

Upon return to the United States, the patient consulted me and a diagnosis of early pregnancy was made. The last menstrual period had been in August, 1953. The operative wound appeared healed and the uterus normal except for some irregularity in contour. The pregnancy progressed normally except for extreme apprehension on the part of the patient until life was felt. Following this, less nervousness and apprehension were noted. Bouts of crampy abdominal pain occurred at times and hospitalization was required on several occasions. These pains were ascribed to the adhesions from the previous operation.

On May 8, 1954, two weeks prior to the expected date of confinement, a laparotomy was performed. After separation of numerous adhesions, the uterus was finally exposed and found to be deformed and flattened along the right wall. Four loops of ileum were firmly adherent to the right cornual area; this finding apparently explained the abdominal pains. A living female infant who weighed 2,936 grams was delivered by classical section and the uterus was thoroughly inspected. In the right cornual region there was found a 3 by 3 cm. area in which no uterine muscle was present. Only mucosa constituted the wall covered by the previously adherent bowel. There were other smaller areas, two in number, where the mucosa constituted the entire thickness of the uterine wall. Fibroids were present on the posterolateral wall measuring approximately 3 by 3 cm. The right ovary was found embedded in the lateral uterine wall.

A total hysterectomy was done with preservation of the left adnexa. The patient made an uneventful recovery and was discharged on the sixth postoperative day. Follow-up visits showed her to be well with no complaints. The infant is gaining weight and making normal progress.

The smaller laceration caused by interstitial gestation of under ten weeks' duration may be handled by wedge resection. Older pregnancies are perhaps better treated by hysterectomy unless there are compelling reasons, such as nulliparity, for conservatism.

Felmus and Pedowitz[15] report that the only fatality in their series occurred in a case where the operation was reconstructive in nature. Thus the conservative procedure may itself be more hazardous. Our case demonstrates that pregnancy can occur in an extensively reconstructed uterus, but that there is then danger of rupture of the uterus.

Perhaps in this case the rapid closure at the time of the first operation resulted in a relatively poor approximation of the tissues, permitting the occult rupture. Had complete rupture occurred in our case, it is believed that the bowel adhesions would have caused serious technical difficulty.

Summary

A case of occult rupture of the uterus following extensive laceration due to ruptured interstitial pregnancy is presented with outcome and findings at laparotomy.

References

1. Mathieu, A., and Wilson, W.: Surg., Gynec. & Obst. **55**: 640, 1932.
2. Wynne, H. M. N.: Bull. Johns Hopkins Hosp. **30**: 15, 1919.
3. Wynne, H. M. N.: Am. J. Surg. **32**: 389, 1929.
4. Kerr, J. M.: Operative Midwifery, London, 1908, Baillière, p. 560.
5. Rosenthal: Zentralbl. Gynäk. **20**: 1297, 1896.
6. Ballantyne, E., Murray, K., and Frazer, R.: Canad. M. A. J. **43**: 560, 1940.
7. Richardson, L.: Lancet **2**: 296, 1930.
8. Morris, Henry: Human Anatomy, ed. 10, Philadelphia, 1943, The Blakiston Company, pp. 1470-1472.

9. Webster, J.: Ectopic Pregnancy, New York, 1895, The Macmillan Company, p. 76.
10. Schumann, E.: Extra-Uterine Pregnancy, New York, 1921, D. Appleton & Co.
11. Curtis, A.: Surg., Gynec. & Obst. **26**: 551, 1918.
12. Kelly, H. A.: Operative Gynecology, New York, 1902, D. Appleton & Co., vol. 2, p. 434.
13. Farrar, L. K. P.: Am. J. Obst. **79**: 733, 1919.
14. Hyams, M. N.: AM J. OBST. & GYNEC. **65**: 697, 1953.
15. Felmus, L. B., and Pedowitz, P.: AM. J. OBST. & GYNEC. **66**: 1271, 1953.
16. MacFarland, K. T., and Sparling, D. W.: AM. J. OBST. & GYNEC. **51**: 343, 1946.
17. Crawford, E., and Hutchinson, H.: AM. J. OBST. & GYNEC. **67**: 568, 1954.

TANTALUM MESH REPAIR OF VENTRAL HERNIA FOLLOWED BY TERM PREGNANCY AND DELIVERY

ALBERT B. BROWN, M.D.,* AND AMOS R. KOONTZ, M.D., BALTIMORE, M.D.

(From the Departments of Gynecology, Obstetrics, and Surgery of The Johns Hopkins University)

SINCE the introduction of tantalum gauze in the repair of large ventral hernias in 1948,[1-3] there have been many reports proving its usefulness. There have been very few cases, however, of term pregnancy following the use of a large piece of tantalum gauze applied to the abdomen for the repair of a hernia. So far, we have been able to locate only two such cases, the first of which was reported by Barrow[4] in 1953. This was the case of a 25-year-old girl who had a large abdominal defect repaired with tantalum mesh, after which she became pregnant and delivered twins. There was no recurrence of the hernia two years later. A second case is known to us in which a full-term pregnancy was delivered following a tantalum-mesh repair of an abdominal hernia. The outcome of this case was also quite satisfactory. The purpose of this paper is simply to report a third case, the outcome of which was also very satisfactory.

F. O. R. (J. H. H. No. 619058), a 30-year-old white patient, was seen for the first time at The Johns Hopkins Hospital on Sept. 23, 1952, at which time she appeared in the Gynecological Out-patient Department. At that time she was complaining of a ventral hernia which had been present since the age of 8 years. In 1949 the hernia had been repaired. The repair had held up for one year and then the hernia recurred and was worse than before operation.

Physical examination in September, 1952, showed that she was very obese (weight 304 pounds) and short (5 feet, 3 inches), with a large panniculus of fat and hernia hanging from the anterior abdomen, somewhat resembling an apron. The hernia sack in the middle of the panniculus was large and the hernial ring appeared to be located somewhat below the umbilicus and to measure about 6 cm. in diameter.

The patient was advised that she should lose weight before surgery would be undertaken. She was referred to the Food Clinic where she was placed on a 1,500 calorie diet. She was very cooperative about dieting and by April of 1953 she has lost 77 pounds and weighed 227 pounds. At this point she was admitted to hospital for repair of the hernia.

On April 20, 1953, this patient was taken to the operating room where, under gas-oxygen-ether anesthesia, the large panniculus was removed by a transverse incision. About 15 to 20 pounds of fat was removed by this procedure. The hernial sack was opened and was found to measure about 16 cm. in diameter and contained omentum and intestine. The omentum was removed to facilitate reduction of the hernia. The opening into the abdomen measured about 6 cm. in diameter. The fascia around the hernial ring was quite attenuated. An imbrication type of repair of the hernia was carried out in the Mayo fashion. Although the opening into the abdomen had been closed, it was felt that the abdominal wall should be reinforced by a large sheet of tantalum gauze because of

*Present address, Department of Obstetrics and Gynecology, University of Saskatchewan, Saskatoon, Sask.

the attenuation of the surrounding fascia and the history of failure of a previous repair. Accordingly, a piece of tantalum gauze measuring 6 by 12 inches was placed over the site of repair of the hernia. As is usual after the use of a large piece of mesh, the wound was drained. Her postoperative course was uneventful.

At her checkup six weeks postoperative the abdomen was well healed and there was no evidence of recurrence of the hernia. It was also noted that she was amenorrheic but, due to her obesity, it was difficult to outline the uterus. It was presumed that the amenorrhea was due to the disturbance of the operation.

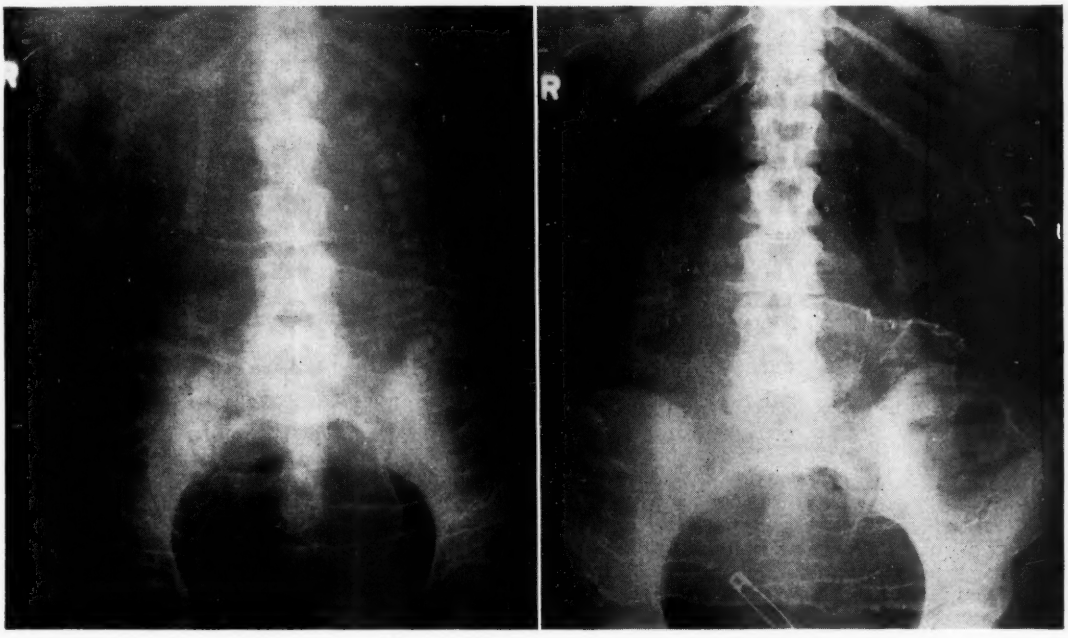


Fig. 1. Fig. 2.

Fig. 1.—X-ray of abdomen prior to delivery.
Fig. 2.—X-ray of abdomen taken post partum.

She was seen in the Gynecological Out-patient Department the next time in December, 1953, at which time she was complaining of abdominal enlargement and was quite apprehensive about a possible recurrence of the hernia. At this time she was found to have an 8 months' pregnancy in the abdomen and there was no evidence of recurrence of the hernia. She was then referred to the Obstetrical Out-patient Department where she was found to be a para i-0-0-i whose last child had been born in 1944. Her last menstrual period was noted to have been on April 1, 1953, giving her an expected date of confinement of Jan. 8, 1954. Aside from the obesity (214 pounds) and the history of previous hernia repair, her pregnancy was considered as being normal. An x-ray was taken of the abdomen prior to delivery (Fig. 1). On Jan. 6, 1954, she was spontaneously delivered of a 4,400 gram male infant in good condition after a labor totaling 26 hours and 8 minutes. The labor was rather long due to poor uterine contractions but otherwise can be considered normal. Examination of the abdomen post partum disclosed no evidence of hernia. Another x-ray was then taken of the abdomen (Fig. 2).

It should be noted that the hernia repair was carried out on April 20, and that the last menstrual period was April 1. From this, one would assume that, at the time the tantalum was applied, this patient was perhaps 6 days pregnant.

When the patient was at term, even with this large infant, there did not seem to be any undue discomfort as a result of the abdominal enlargement. It appears that the extra abdominal wall was derived by stretching of the upper abdominal wall.

In the figures some cross striations in the tantalum mesh can be seen which are probably nothing more than folds. However, if the x-rays are examined closely, there are areas in which the mesh has undoubtedly torn. This does not seem to influence the success of the repair as the tantalum acts as a scaffolding for the fibroblasts to grow in. These, in turn, form the layer which builds up a firm abdominal wall. In practically all cases the tantalum gauze breaks sooner or later as a result of repeated bending. Indeed, it has been shown that a piece of tantalum mesh will break if it is bent 400 times.[5]

In spite of the satisfactory outcome of this case, and the two others referred to in this article, we do not think that all patients who have had such a repair should be allowed to become pregnant. It is advisable for the cases to be individualized. For example, sterilization at the time of herniorrhaphy might be carried out if the patient already has her family, if the hernial defect is very large, and especially if there have been several attempts at repair. It is probably justifiable, however, to allow a patient to become pregnant if she is desirous of having children and if a satisfactory operation has been carried out.

Summary

A case is reported of a large abdominal hernia which was repaired by tantalum gauze. Since repair, the patient has been delivered of a full-term pregnancy. The outcome of the case has been entirely satisfactory in all respects.

References

1. Koontz, A. R.: South. M. J. **41**: 214, 1948.
2. Koontz, A. R.: Ann. Surg. **127**: 1079, 1948.
3. Koontz, A. R.: South. M. J. **42**: 455, 1949.
4. Barrow, D. W.: J. Kentucky M. A. **51**: 477, 1953.
5. Koontz, A. R., and Kimberly, R. C.: Ann. Surg. **137**: 833, 1953.

PYOCOLPOS AND PYOMETRIUM IN A CHILD

DONALD W. SPRATT, M.D., ROCHESTER, N. Y.

(From the Department of Gynecology of the Rochester General Hospital)

ALTHOUGH many cases of pyometrium have been reported in the past,[1] the majority of them have been associated with carcinoma of the uterus, either cervical or fundal, or due to stenosis of the cervix as a result of aging or trauma. A review of the American literature for the past fifteen years did not uncover a case similar to the present one, although they must have undoubtedly occurred.

Case Report

S. H., an 11-year-old girl, was in good health until about one month prior to the present illness. Her menarche had occurred some eighteen months previously, and periods had been regular although slight to moderate in amount. One month before, she had complained of a vaginal discharge and dysuria, and had been treated with a sulfonamide preparation orally with complete relief.

For two or three days prior to admission, the child had again noted dysuria and a rather profuse vaginal discharge associated with frequency and urgency. On the morning of admission, she was again started on the sulfonamide by her family physician. About 2:30 P.M., however, she was unable to void and was in severe pain from distention of the bladder. She was seen in the Emergency Room where examination showed the temperature to be 98.8° F. rectally, pulse 80, respirations 20, and blood pressure 120/50. The bladder was distended to reach half the distance to the umbilicus, there was a moderate, foul, mucopurulent vaginal discharge with inflammation of the introital area, and rectal examination was said to have shown the cervix to be extremely tender to pressure and movement.

Catheterization yielded 800 c.c. of urine showing 0 to 3 white blood cells and 8 to 13 red blood cells per high-powered field. There was no albumin or sugar present. The white blood count was 13,500 at this time. The vaginal smear was negative for specific disease. Intravenous pyelograms were impossible due to lack of cooperation from the patient. No foreign bodies were noted on a flat film of the abdomen.

The child was allowed to go home after this episode; however, she was readmitted at 8:00 P.M., again with complete urinary retention, severe cramping, lower abdominal pain, and low backache. Temperature, pulse, respirations, and blood pressure were still normal. The abdomen was soft, but the bladder was distended and tender. A Foley catheter was inserted, 500 c.c. of clear urine obtained, and the catheter left in place. No masses were palpable after this, and peristalsis was active. Laboratory studies at this time showed the nonprotein nitrogen to be 25 mg. per cent, urea nitrogen 6 mg. per cent, red blood count 4.97 million, hemoglobin 13.1 Gm. or 90 per cent, color index 0.90, and white blood count 9,600.

She was first seen in consultation the afternoon after admission. At this time the urine was clear and draining well through the catheter. The abdomen was voluntarily resistant and slightly tender in the lower quadrants. The presence of a lower abdominal mass was questionable and could not be outlined. Rectal examination was impossible due to lack of cooperation; however, a marked, foul vaginal discharge was obvious, and examination under anesthesia was advised.

Under anesthesia, examination showed an essentially intact hymen with a pin-point opening in its right upper portion, from which yellow-green pus could be expressed with pressure on the perineum. Rectoabdominal examination showed the true pelvis almost completely filled with the markedly distended vagina, and the enlarged uterus extended to the umbilicus. The uterus was freely movable and no adnexal masses were palpable. Following this examination, the patient was prepared and draped and a portion of the hymen excised. This allowed the escape of about 1,000 c.c. of very foul pus which culture showed to be predominantly hemolytic *Staphylococcus albus*. After slow release of the pus, the cervix was found to be widely dilated, and the vagina and uterus formed a single, large cavity. A small gauze drain was inserted to prevent the hymen from closing.

Postoperatively the patient was placed in Fowler's position, a Foley catheter was maintained on constant drainage, she was given 300,000 units of aqueous penicillin twice daily, analgesics, and mild sedatives. Her temperature, which had been normal preoperatively, averaged about one-half of a degree lower after drainage. The catheter was removed in 24 hours and the patient allowed up. There were no further urinary complaints. The drain was removed in 48 hours and the patient was discharged on the third postoperative day completely asymptomatic.

Examination two months postoperatively was difficult, but the uterus seemed to be of normal size and the adnexal areas negative. A normal period had occurred about one month after operation.

Comment

The sequence of events leading to the findings in this case are presumed to have been as follows: Probably the patient developed a hematocolpos as a result of occlusion of the minute hymenal aperature due to agglutination or infection. With organisms previously introduced through this opening now trapped in a collection of blood, they proceeded to produce a pyocolpos with gradual extension to involve the uterine cavity. As the pressure increased, urinary symptoms followed, and finally the sealed opening broke down to allow the escape of the "vaginal discharge."

The lack of discernible tubal involvement is difficult to explain. It may have been due to occlusion of the isthmic portion of a congenital or inflammatory nature. This lack of involvement did obviate the need for laparotomy, as advised by Tompkins[2] in all such cases where it is present.

The future of this child's tubal function is necessarily a matter of some concern. In view of the lack of palpable tubal enlargement, essentially afebrile course, and negative pelvic examination at two months, her prognosis should be fair. Pregnancy has occurred following similar findings which were due to a hematometrium.[3]

References

1. Carter, B., Jones, C. P., Ross, R. A., and Thomas, W. L.: Am. J. Obst. & Gynec. 62: 793, 1951.
2. Tompkins, P.: J. A. M. A. 113: 913, 1939.
3. Searle, W. N.: J. Obst. & Gynaec. Brit. Emp. 44: 729, 1937.

16 North Goodman Street,
Rochester 7, New York

A FLEXIBLE INSTRUMENT FOR CURETTING THE INTERPOSED UTERUS

SAMUEL S. ROSENFELD, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology of the Lebanon and Jewish Memorial Hospitals)

A SERIOUS objection to the interposition operation has been the fact that when an indication for curettage arose great difficulty was encountered in performing the operation and the uterus was not infrequently perforated in the attempt.

The standard endometrial curette could hardly be expected to follow the almost horizontal position that the well-placed interposed uterus usually assumes and the flexible curettes now obtainable fail more often than they succeed.

To those of us who have performed the interposition operation consistently through the years and are acquainted with its excellent results, the difficulty in curetting such a uterus has been a source of deep concern. The flexible curette* here described was designed in an effort to overcome this drawback.

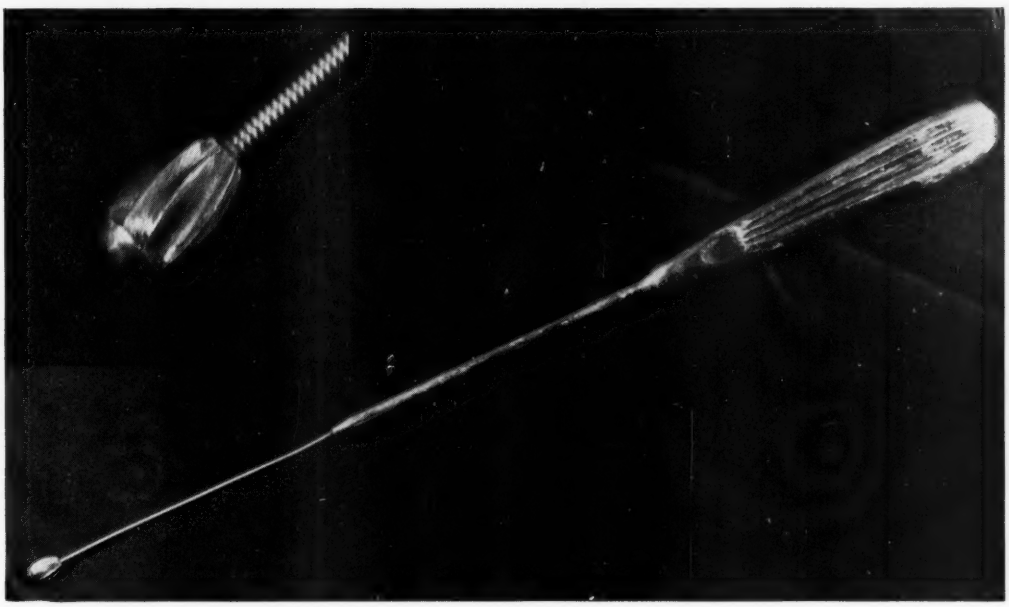


Fig. 1.—Flexible curette. Insert illustrates cutting head.

The basic idea in the design of this instrument is a shaft made flexible by employing reinforced spring steel. To this spiral spring an egg-shaped oval curette head made of tooled steel with longitudinal cutting edges is firmly soldered. The flexible shaft and the oval curette head readily follow the direction of the endometrial cavity.

*This curette was made by Messrs. Grimm and Norton, 240 East 26th St., New York, New York.

After the curette is introduced into the endometrial cavity it is manipulated clockwise and tissue in adequate amounts for diagnosis can usually be found adherent to the concavities between the longitudinal cutting edges. Additional tissue is gathered from a gauze flat that is carefully placed on the posterior vaginal wall prior to curetting. I have also obtained adequate amounts of tissue with this instrument when employing the orthodox vertical up and down or back and forth motion as in the standard technique for curettage.

The over-all length of the curette is 11 inches. The spiral spring is 3½ inches in length. The length of the cutting head is ⅜ inch and contains 7 longitudinal cutting edges. The head of course can be made larger or smaller than this model and the cutting edges can be increased or decreased as desired.

Department of Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Selected Abstracts*

Journal of the American Geriatrics Society

Vol. 3, No. 2, February, 1955.

Tyler, Frank H., Eik-Nes, Kristen, Sanberg, Avery A., Florentin, Angel A., and Samuels, Leo T.: Adrenocortical Capacity and the Metabolism of Cortisol in Elderly Patients, p. 79.

Elman, Robert: Surgical Experience in the Aged as an Aid to Surgery in the Young, p. 85.

Hunnicutt, Arthur J.: Physiologic Reserves in the Aged: Application to Operability, p. 93.

The Journal of Clinical Endocrinology and Metabolism

Vol. 15, No. 2, February, 1955.

*Green, S., Evans, J. M., and Hertz, R.: Acyclic Menstrual Bleeding Associated With Erythrocytosis, p. 199.

*Abramson, D., and Reid, D. E.: Use of Relaxin in Treatment of Threatened Premature Labor, p. 206.

Green, Evans, and Hertz: Acyclic Menstrual Bleeding Associated With Erythrocytosis, p. 199.

Excessive acyclic menstrual bleeding associated with polycythemia is a rare occurrence. Such a case is reported by the authors. Polycythemia may occur either in response to some known stimulus, in which case it is termed erythrocytosis, or it may be of unknown etiology and then it is called erythemia. Both conditions may be complicated by thrombosis and hemorrhage.

The relationship of the pituitary and hypothalamic area to polycythemia and possibly to the acyclic uterine bleeding is discussed.

J. EDWARD HALL, M.D.

Abramson and Reid: Use of Relaxin in Treatment of Threatened Premature Labor, p. 206.

The authors present the cases of 5 women who entered the hospital between the twenty-ninth and thirty-first weeks of pregnancy and whose labor ceased after the intramuscular administration of relaxin. Pregnancy in each case continued to at least the thirty-sixth week with the delivery of a normal infant.

No conclusions are drawn from this short series, but it is presented to stimulate the use of relaxin by other workers.

J. EDWARD HALL, M.D.

Vol. 15, No. 4, April, 1955.

Mendelsohn, M. L., and Pearson, D. H.: Water and Salt Metabolism After Bilateral Adrenalectomy in Man, p. 409.

Diczfalusy, E., and Loraine, J. A.: Sources of Error in Bioassays of Serum Gonadotropin, p. 424.

*Whitelaw, M. J., and Escamilla, R. F.: Sublingual Ergot Alkaloids in Control of Vasomotor Flushes, p. 487.

Whitelaw and Escamilla: Sublingual Ergot Alkaloids in Control of Vasomotor Flushes, p. 487.

The vasomotor flushes or "hot flashes" are common during the climacterium. These are usually relieved by the administration of estrogens but estrogens are contraindicated in some women. Since these flushes are undoubtedly due to instability of the vegetative nervous system the authors treated 40 women with hydrogenated ergot alkaloids because of their known action on the vegetative nervous system.

Two sublingual tablets of 0.5 mg. each were administered four times a day. Of the 40 patients, 2 had "excellent" relief, 22 "good" relief, 13 partial relief, and 3 no relief. Placebos were given to the 22 "good" relief patients with a recurrence of symptoms in 12, and a regression to partial relief in 6.

J. Edward Hall, M.D.

New York State Journal of Medicine

Vol. 54, No. 22, November 15, 1954.

*Sheffery, Joseph B.: A Method of Determining Tubal Patency and Tubal Ciliary Activity, p. 3092.

Sheffery: Tubal Patency and Tubal Ciliary Activity, p. 3092.

The author notes the importance of tubal ciliary activity in the process of tubal transportation of the ovum. Since no tests are presently available to determine this function, he suggests the following technique which he has carried out in 26 patients. From 2 to 7 days after the cessation of the menstrual flow the patient is seen in the office or hospital. After a cleansing douche, the cervix is visualized with a speculum wet with tap water. A screw-type cannula is introduced into the cervical canal and 10 c.c. of sterile saline containing a small amount of indigo carmine is injected into the uterine cavity. After 3 to 4 minutes the cul-de-sac is punctured with a 22 or 24 gauge long spinal needle. If colored saline is not recovered from this puncture it is presumed that the tubes are obstructed and further tubal patency studies are required. If saline is recovered, 8 to 10 c.c. of a sterile solution consisting of neutral olive oil (29.5 per cent), distilled water (70 per cent), and a stabilizer warmed to body temperature is injected very slowly into the cul-de-sac. The needle is then removed and a dry cotton tampon placed firmly against the puncture site and the screw cannula removed from the cervix. On the third or fourth day after this procedure the patient is re-examined, again using instruments free of any fatty substance. The cervix is aspirated, the secretions placed on a glass slide and stained with sudan III, a selective fat stain. Under the microcope, if oil droplets are seen, it is interpreted that the fluid currents of the pelvic peritoneum have directed the oil solution to the tubes and that the ciliary current in the tubes has carried the oil particles into the uterus. This confirms the ability of the tubal cilia to transport the ovum. The author emphasizes the sensitivity of this test and notes all instruments and material must be grease free and should be flamed before use in order to assure this. The cul-de-sac puncture has not leaked in any of the 26 reported cases and is not a source of error. This test is useful as a screening mechanism and may also be of significant value in individuals who have undergone tuboplasty with resultant patent tubes but continued infertility.

Stewart A. Fish, M.D.

The Practitioner

Vol. 172, February, 1954.

Lawrence, R. D.: The Diabetic Association, p. 174.
Anning, S. T.: Post-partum Phlegmasia Dolens: An Historical Study, p. 177.

Vol. 172, April, 1954.

Bishop of Rochester: The Church and Sex, p. 350.
Learoyd, C. G.: The Problem of Homosexuality, p. 355.
Neustatter, W. Lindesay: Homosexuality: The Medical Aspect, p. 364.
*Swyer, G. I. M.: Homosexuality: The Endocrinological Aspects, p. 374.
Maude, John: Homosexuality and the Criminal Law, p. 378.
Bennett, Reginald: The Problem of Prostitution, p. 381.
*Malleson, Joan: Sex Problems in Marriage—With Particular Reference to Coital Discomfort and the Unconsummated Marriage, p. 389.
Stafford-Clark, David: The Etiology and Treatment of Impotence, p. 397.
Barnes, Josephine: The Unmarried Woman, p. 405.
Walker, Kenneth: The Celibate Male, p. 411.
Torrie, Alfred: Pre-marital Chastity, p. 415.
Griffith, Edward F.: Sex Problems of Adolescence, p. 420.
Spence, A. W.: Sexual Adjustment at the Climacteric, p. 427.
Amulree, Lord: Sex and the Elderly, p. 431.
Pearce, J. D. W.: Problems of Sex in the Services, p. 436.
Curran, Desmond: Sexual Perversions, p. 440.
Popkess, Captain Athelstan: Some Criminal Aspects of Abnormalities of Sex. p. 446.

Swyer: Homosexuality, p. 374

The capacity for sexual response is not primarily dependent upon the sex hormones and the direction of sexual development is influenced mainly by psychological and environmental conditioning. The levels of sex hormones appear to do little more than modify the intensity of sexual activity. There is no convincing evidence that human homosexuality is dependent upon hormonal aberrations. The use of sex hormones in the treatment of homosexuality is mainly disappointing.

A. ROSENTHAL, M.D.

Malleson: Sex Problems in Marriage, p. 389.

Vaginismus is the principal cause for dyspareunia. Cure is effected by instructing the patient in self treatment, particularly in the use of glass dilators. Surgery is not indicated.

A. ROSENTHAL, M.D.

Vol. 173, August, 1954.

Robb-Smith, A. H. T.: The Concept of the Collagen Diseases, p. 117.
Logan, W. P. D.: Morbidity Statistics From General Practice, p. 188.
Schroeder, Henry A.: Hydralazine in the Control of Severe Hypertension, p. 195.

Vol. 173, September, 1954.

Neale, A. V.: Jaundice in the Newborn, p. 240.

Vol. 173, October, 1954.

*Tenney, Benjamin: Advances in Obstetrics and Gynaecology, p. 360.
Evans, Frankis T.: Advances in Anaesthesia, p. 433.

Tenney: Advances in Obstetrics and Gynaecology, p. 360.

Considerable work is being done on the use of hypotensive drugs during the antenatal period and it appears that they are of value in essential hypertension in pregnancy. In the treatment of diabetes complicating pregnancy the use of large doses of hormones has still to prove its efficacy. Delivery of the fetus by cesarean section at the thirty-fourth to the thirty-sixth week of pregnancy is the treatment of choice. In heart disease complicating pregnancy it is generally accepted that delivery per vaginam, with shortening of the second stage by the use of obstetrical forceps, is the safest method. A patient who has shown any sign of failure should be on complete bed rest, preferably in a hospital, for the remainder of the pregnancy. Afibrinogenemia is now a well-recognized entity most generally developing after premature separation of the normally implanted placenta. Treatment should include early recognition, delivery of the fetus and placenta, and the administration of 2 to 6 Gm. of fibrinogen. The use of the Papanicolaou vaginal smear as a screening process for the detection of carcinoma of the cervix, however, except in the noninvasive form, still remains a difficult problem. Dysmenorrhea is still a difficult condition to treat and except for the use of estrogens for menopausal symptoms and conditions the use of hormones is largely disappointing.

A. Rosenthal, M.D.

Southern Medical Journal

Vol. 47, No. 9, September, 1954.

St. Martin, E. C., Pasquier, C. M., Jr., and Campbell, J. H.: Ureteral Complications of Radical Surgery for Carcinoma of the Cervix, p. 832.

Ware, H. Hudnall Jr.: The Treatment of Endometriosis, p. 865.

*Rogers, Stanley F., Moyer, John H., Hughes, Warren M., and Moore, Jack: Drug Therapy in the Management of Pregnancy Toxemia, p. 871.

Rogers, Moyer, Hughes, and Moore: Drug Therapy in the Management of Pregnancy Toxemia, p. 871.

In an attempt to evaluate some of the newer hypotensive drugs in the toxemias of pregnancy, 38 patients with pre-eclampsia or eclampsia were observed in this study. All patients were admitted to the hospital and lightly sedated with barbiturates for 48 hours. On this regime 20 of the 38 patients showed clinical improvement and thus hypotensive drug therapy was not warranted. In the remaining 18, hexamethonium alone or in combination with hydralazine was used in an effort to lower the blood pressure. The parenteral route was selected and the therapeutic objective was to regulate the systolic blood pressure as close to 130 mm. of mercury as possible by titration of the rate of drug infusion. The glomerular filtration rate, renal blood flow, and electrolyte excretion were determined in 7 patients. The authors observed that hexamethonium alone was most beneficial in those patients who had previous essential hypertension. It was also useful in controlling tachycardia in patients receiving hydralazine. Patients who did not respond to hexamethonium alone were also given hydralazine, and prompt, dramatic, hypotensive response was observed. Since the series is small no statistically significant correlation of fetal and maternal survival can be made. The authors believe that these drugs have little effect on the length of labor. Parasympathetic blockade with large doses of hexamethonium may be detrimental to the infant by causing ileus or bladder distention and the authors suggest that newborn infants of mothers treated with these drugs should have their bladders and stomach emptied immediately after birth as the amniotic fluid contains a high concentration of hexamethonium. There was no improvement in renal function associated with the reduction in blood pressure in any of the patients studied. The authors conclude that hypotensive drugs may be useful in resistant cases of toxemia of pregnancy but they should be used only as supplements to the standard methods of therapy employed at the present time.

Stewart A. Fish, M.D.

Correspondence

Extractor Instead of Forceps

To the Editors:

I read with a great deal of interest the article, "Extractor Instead of Forceps," by Viktor Finderle, which appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in May, 1955.

Both Dr. Richard Torpin and I have discussed some such mechanism for quite a while and have sent the working models which we have produced (Figs. 1 and 2) to the Medical Museum, Walter Reed Army Medical Center, Washington 25, D. C.

Fig. 1.

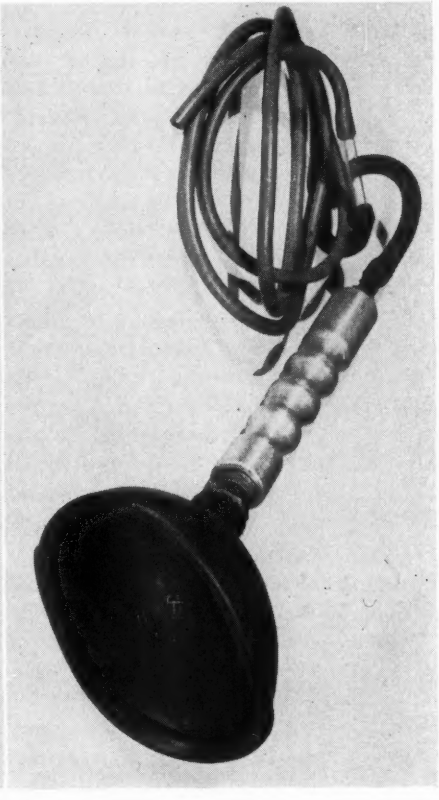


Fig. 2.

Fig. 1.—Type of extractor devised by Dr. Richard Torpin.
Fig. 2.—Type of extractor devised by Dr. Mario A. Castallo.

Our experience with these extractors was not as successful as Dr. Finderle's with the one explained in his article, but perhaps we were not using them correctly; I see that Dr. Finderle uses them with only light analgesia and with the patient's powers supplementing the extractor.

J. Y. Simpson thought of this method of delivery back in 1849, so there truly seems little new under the sun.

The bibliography of the Finderle article is a very extensive one and anyone interested will find a great deal of information on this method of delivery.

MARIO A. CASTALLO, M.D.

1621 SPRUCE STREET
PHILADELPHIA 3, PENNSYLVANIA
JUNE 24, 1955

Treatment of Cancer of the Endometrium

To the Editors:

The July, 1955, JOURNAL contains an article by John M. Sadler, entitled "Problems Associated With Treatment of Cancer of the Endometrium," which I wish to discuss. I agree with the author that satisfactory results are achieved in many cases of carcinoma of the corpus by surgery, and that surgery may be the treatment of choice in good-risk patients although, in my opinion, it is advisable to apply radium in the vagina postoperatively to prevent vaginal metastases or recurrences.

Many authors have shown, as has Dobbie recently, that such recurrences develop in about 10 per cent of cases of corpus cancer radically operated upon. Such recurrences may sometimes appear for the first time several years after treatment. The author states, "The follow-up on all cases is based on recurrence of tumor in one to three years rather than five-year survival rates," and he refers to statements by Finn and Speert. Many authors have pointed out that five-year survival rates are of less importance in cases of corpus carcinoma than in cases of carcinoma of the cervix. In this respect I refer to the discussion at the International Congress in New York in May, 1950. It seems questionable, therefore, if any conclusions can be drawn from the series presented as to the surgical results.

I cannot agree with the author that the results with x-ray and radium therapy alone are poor. It is remarkable that the author recommends a radical hysterectomy with pelvic lymphadenectomy in carcinoma of the corpus, a treatment which has been advocated by some surgeons in recent years, but for radiation therapy uses radium sources in the uterine cavity which are inaccurate as to placement and distribution, as the author himself states. No conclusions can be drawn from such a treatment. Radiotherapy of today is not the radiotherapy of twenty-five years ago.

As early as 1932 Heyman demonstrated that the insertion of one, two, or a few radium tubes in the uterine cavity in cases of carcinoma of the corpus is a very inaccurate treatment which may be applied only as a palliative measure. Many authors have confirmed this observation. A satisfactory radiation treatment is achieved only if attention is given to the anatomical findings and the treatment applied considers the physical laws. This is achieved by a packing of the uterine cavity with multiple sources as recommended in 1936 by Heyman or by a modification of this treatment as described by Ries, Nolan, Weghaupt, Strickland, Lowbeer, and others. Such radiation therapy will lead to satisfactory results, and only from such therapy may conclusions be drawn as to the value of x-ray and radium therapy in the treatment of carcinoma of the corpus. It is as yet too early to conclude from the results presented whether surgery or radiotherapy or radiotherapy plus surgery is the treatment of choice in good-risk patients, but it is obvious that radiation therapy which fulfills the requirements of a curative treatment is the therapy of choice in poor-risk patients.

The author points out, "There is danger of perforation of the uterus and of spread of infection or tumor cells." I agree that a perforation may sometimes occur at the time of curetting and also during the insertion of radium sources into the uterine cavity if these procedures are carried out by doctors who have limited experience in using gynecological instruments. The packing of the uterine cavity with multiple sources as well as

the radical hysterectomy should be carried out by skilled gynecologists. At the Radiumhemmet we have used this method of treatment in about 2,300 cases and have seen complications as pointed out by Dr. Sadler only in very rare instances.

The staging of adenocarcinoma of the endometrium as presented by the author is of value in presenting surgical results but cannot be used as a clinical staging prior to treatment. Such a classification is necessary if conclusions are to be drawn from therapeutic statistics. As far as pelvic lymph node metastases are concerned, it is necessary to distinguish a carcinoma of the corpus from a carcinoma of the corpus and endocervix. In this respect I refer to the valuable contribution by Liu and Meigs in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

Finally, the author points out, ''. . . it is generally accepted that 6,000 gamma r is necessary to eradicate a tumor cell.'' Even if it is true that it is necessary to apply a dosage of 5,000 to 6,000 r tissue roentgens in six to eight weeks in cases of carcinoma of the head and neck, this has not been proved as far as pelvic tumors are concerned, in which cases the volume of tissue treated is much greater. Experimental investigations have shown that the peripheral parts of a carcinoma have a greater sensitivity than the central parts.

H. L. KOTTMEIER, M.D.

RADIUMHEMMET
STOCKHOLM 60, SWEDEN
AUGUST 5, 1955

Reply by Dr. Sadler

To the Editors:

I wish to thank Dr. Kottmeier for his comments. We are all envious of the excellent results with radiation therapy at the Radiumhemmet. However, I would like to re-emphasize several points.

As stated in my article, we were well aware that our methods of intrauterine radium therapy were inadequate and it was for this reason that the study was undertaken and the method discontinued. I also mentioned that multiple small sources in the uterus would provide much less penetration than the gamma r from the larger 100 mg. source. No doubt the endometrial lining would receive a more evenly distributed irradiation but less penetration when the small multiple sources are used. Reports from some of the best clinics in this country (Scheffey and others), at present using multiple-source techniques, indicate a reduction in the incidence of viable tumor cells in the irradiated surgically removed specimen, but state that 50 per cent of the uteri still contain viable tumor. It is for this reason that we feel radium therapy alone is poor.

With modern surgical techniques and modern anesthesia, the number of poor-risk patients has become smaller and smaller. If we use radium alone, we would have to assume that 50 per cent of these patients still have viable tumor cells in the uterus, so that the risk of a total hysterectomy without node dissection would seem less than allowing the uterus to remain in situ with viable tumor in the ''poor-risk'' patient.

JOHN M. SADLER, M.D.

100 BROUGHTON ROAD
PITTSBURGH 34, PENNSYLVANIA
SEPTEMBER 12, 1955

Further to Reduce Perineal Discomfort in the Puerperium

To the Editors:

I was much interested in the article in your issue of July, 1955, by Dr. Fred Haufrect on ''A Procedure to Reduce Perineal Discomfort in the Puerperium,'' but wish that he had gone somewhat further in this essay to minimize the discomfort of the results of childbirth, especially where the perineum has been repaired.

Even with modern methods of early rising after delivery and plastic repairs of the female genital tract, the greater part of the patient's time is still spent in bed and certainly for the first few days most meals are taken thus. His description of the advantages of sitting on the tuber ischii is perfectly correct and can be applied to the patient in bed as well as when she is sitting up.

The secret, as I have pointed out in lectures to nurses in the Rotunda Hospital, Dublin, is that the patient should balance herself on the tuber ischii and then allow all her muscles to relax so that the superficial perinei, in particular, should cease to pull on the damaged skin edges. This also applies to her position in bed. She should be taught to raise herself on her hands in the bed and then to swing her buttocks toward the top of the bed when she is in a balanced position. Then, and then only, should the pillows be placed around her to support her back.

In Fowler's position or if the pillows are already awaiting her back, there is a tendency for the patient to slip down in the bed, thus drawing the perineal skin backward and causing actual pain.

It is not easy to explain this position to a patient and the best method is a practical demonstration. The reward lies in the change from an anxious, disbelieving face to the pleased and comfortable smile that shines forth when the patient finds that it really does work.

For the immediate postpartum period there are only two comfortable positions, either lying on the side or else sitting bolt upright. In both cases complete relaxation of muscles is the essential.

HENRY FITZGIBBON, M.D., M.A.O.
VISITING ASSISTANT, ROTUNDA HOSPITAL, DUBLIN, ETC.

296 METCALFE STREET
OTTAWA, ONTARIO
SEPTEMBER 2, 1955

Correction by Dr. McCormick

To the Editors:

The second paragraph of my discussion of the paper by Drs. Dieckmann and Harrod entitled "Breech Delivery at the Chicago Lying-in Hospital, 1945-1952" (page 262 of the August issue of the JOURNAL) was incorrectly reported.

More clearly and correctly stated, it should read as follows:

"While steadying the top of the fundus with one hand, and compressing the presenting pole of the fetus by grasping it with extended fingers and thumb of the other hand, the fetal heart rate is checked by an assistant. If the breech presents, there is no change in the fetal heart rate; while if the head presents, the fetal heart rate decreases as the grasping pressure increases."

Since my associates and I have employed this maneuver for many years, and have found it to be so simple and practical, I would like to pass it on to those who are not familiar with it.

C. O. MCCORMICK, M.D.

621 HUME MANSUR BUILDING
INDIANAPOLIS, INDIANA
AUGUST 27, 1955

INDEX TO VOLUME 70

AUTHORS INDEX*

*July, pp. 1-232; August, pp. 233-466; September, pp. 467-700; October, pp. 701-932; November, pp. 933-1164; December, pp. 1165-1398.

SUBJECT INDEX*

*July, pp. 1-232; August, pp. 233-466; September, pp. 467-700; October, pp. 701-932; November, pp. 933-1164; December, pp. 1165-1398.

D

E

I

J

K

L

R

S

V

W

X

VOL. 70 JULY, 1955 NO. 1

AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

Editors

HOWARD C. TAYLOR, JR. WILLIAM J. DIECKMANN

OFFICIAL ORGAN

THE AMERICAN GYNECOLOGICAL SOCIETY
THE AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
NEW YORK OBSTETRICAL SOCIETY; OBSTETRICAL SOCIETY OF PHILADELPHIA
BROOKLYN GYNECOLOGICAL SOCIETY; ST. LOUIS GYNECOLOGICAL SOCIETY
NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY
THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND
CHICAGO GYNECOLOGICAL SOCIETY; CINCINNATI OBSTETRIC SOCIETY
CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY
WASHINGTON GYNECOLOGICAL SOCIETY
PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
OBSTETRICAL SOCIETY OF BOSTON
LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
SEATTLE GYNECOLOGICAL SOCIETY
SOCIETY OF OBSTETRICIANS AND GYNECOLOGISTS OF CANADA
ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY
KANSAS CITY GYNECOLOGICAL SOCIETY
CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS
NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY
THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY

PUBLISHED BY THE C. V. MOSBY COMPANY, 3207 WASHINGTON BLVD., ST. LOUIS 3, U. S. A.

TABLE OF CONTENTS ON PAGE 6

Vol. 70, No. 1, July, 1955. American Journal of Obstetrics and Gynecology is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States and its Possessions, $15.00 per year; Canada, $15.50; Foreign, $17.00. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.

INDEX NUMBER

VOL. 70 DECEMBER, 1955 NO. 6

AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

Editors

HOWARD C. TAYLOR, JR. WILLIAM J. DIECKMANN

OFFICIAL ORGAN

THE AMERICAN GYNECOLOGICAL SOCIETY
THE AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
NEW YORK OBSTETRICAL SOCIETY; OBSTETRICAL SOCIETY OF PHILADELPHIA
BROOKLYN GYNECOLOGICAL SOCIETY; ST. LOUIS GYNECOLOGICAL SOCIETY
NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY
THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND
CHICAGO GYNECOLOGICAL SOCIETY; CINCINNATI OBSTETRIC SOCIETY
CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY
WASHINGTON GYNECOLOGICAL SOCIETY
PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
OBSTETRICAL SOCIETY OF BOSTON
LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
SEATTLE GYNECOLOGICAL SOCIETY
SOCIETY OF OBSTETRICIANS AND GYNECOLOGISTS OF CANADA
ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY
KANSAS CITY GYNECOLOGICAL SOCIETY
CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS
NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY
THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY

PUBLISHED BY THE C. V. MOSBY COMPANY, 3207 WASHINGTON BLVD., ST. LOUIS 3, U. S. A.

TABLE OF CONTENTS ON PAGE 6

Vol. 70, No. 6, December, 1955. American Journal of Obstetrics and Gynecology is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States and its Possessions, $15.00 per year; Canada, $15.50; Foreign, $17.00. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.